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Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial

Citation for published version:

MRC SUPREMO Trial UK Investigators, Velikova, G, Williams, LJ, Willis, S, Dixon, JM, Loncaster, J, Hatton, M, Clarke, J, Kunkler, IH & Russell, NS 2018, 'Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial', *The Lancet Oncology*, vol. 19, no. 11, pp. 1516-1529. [https://doi.org/10.1016/S1470-2045\(18\)30515-1](https://doi.org/10.1016/S1470-2045(18)30515-1)

Digital Object Identifier (DOI):

[10.1016/S1470-2045\(18\)30515-1](https://doi.org/10.1016/S1470-2045(18)30515-1)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

The Lancet Oncology

Publisher Rights Statement:

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Manuscript Number: THELANCETONCOLOGY-D-18-00578R2

Title: Quality of life at 2-year follow-up of SUPREMO randomised trial of post mastectomy radiotherapy for breast cancer

Article Type: Article (Clinical Trials)

Keywords: breast cancer
radiotherapy
mastectomy
quality of life
patient reported outcomes

Corresponding Author: Professor Galina Velikova, PhD MD

Corresponding Author's Institution: University of Leeds

First Author: Galina Velikova, PhD MD

Order of Authors: Galina Velikova, PhD MD; Linda J Williams, PhD; Sarah Willis, MSc; J Michael Dixon, MD; Juliette Lancaster, FRCR; Matthew Hatton, FRCR; Jacqueline Clarke, FRCR; Ian H Kunkler, FRCR; Nicola S Russell, PhD

Manuscript Region of Origin: UNITED KINGDOM

Abstract: Background Post-mastectomy radiotherapy (PMRT) in patients with 4+ axillary nodes reduces breast cancer mortality, but its role in patients with 1-3 involved nodes is controversial.

Methods BIG2-04-MRC-EORTC SUPREMO is an international parallel randomised controlled trial. Eligible women (over 18 years, with 'intermediate risk' breast cancer, pT1-2N1, pT3N0 and pT2N0 if grade III and/or lympho-vascular invasion, post-mastectomy and axillary surgery) were randomly assigned to receive chest-wall radiotherapy (50 Gy 25 fractions or radiobiologically equivalent 45 Gy 20 fractions or 40 Gy 15 fractions) or not (1:1 ratio). Randomisation was in permuted blocks with varying block length, stratified by centre, without masking of patients or investigators. The primary endpoint is 10-year overall survival. Here, we present the 2-year quality of life (QOL) results (pre-specified secondary endpoint). The QOL substudy, open to all UK patients, consists of questionnaires (EORTC QLQ-C30 and BR23, Body Image Scale, Hospital Anxiety and Depression Scale (HADS) and EQ-5D-3L) completed pre-randomisation, 1, 2, 5 and 10 years. Data were analysed on an intention-to-treat basis, using repeated mixed-effects methods. The trial is registered with International Standard Randomised Controlled Trials (ISRCTN61145589).

Findings

Between August 4, 2006-April 29, 2013, 1688 patients enrolled internationally, 989/1258 (79%) of the UK patients consented to QOL substudy. Patients receiving PMRT reported worse chest-wall symptoms ($p=0.016$) but the difference was small. Symptoms improved from year 1 to 2. Chemotherapy was associated with less improvement. No group

differences were observed for arm symptoms, body image, fatigue, pain, overall QOL, physical functioning or HADS scores. Interpretation PMRT led to more local symptoms up to 2 years post-randomisation, but the difference was small. This data will inform shared decision-making whilst survival results (main trial endpoint) become available.

Funding Medical Research Council, European Organisation for Research and Treatment of Cancer, Cancer Australia, Dutch Cancer Society, Trustees of Hong Kong Shanghai Banking Corporation.

Quality of life at 2-year follow-up of SUPREMO randomised trial of post mastectomy radiotherapy for breast cancer

Short title

Quality of life after post mastectomy radiotherapy

Galina Velikova¹, Linda Jane Williams², Sarah Willis³, J Michael Dixon⁴, Juliette Loncaster⁵, Matthew Hatton⁶, Jacqueline Clarke⁷, Ian H. Kunkler^{8*} and Nicola Russell^{9*} on behalf of the BIG 02-04 MRC EORTC SUPREMO trial investigators

¹ Prof Galina Velikova PhD, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds Cancer Centre, St James's University Hospital, Beckett street, Leeds, LS9 7TF, UK

² Linda Jane Williams PhD, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh UK, Edinburgh, UK

³ Sarah Willis- MSc, London School of Hygiene and Tropical Medicine, Keppel Street, Bloomsbury, Camden, London, WC1E 7HT, UK

⁴ Prof J Michael Dixon MD, Edinburgh Breast Unit, Western General Hospital, Edinburgh, EH4 2XU, UK.

⁵ Juliette Loncaster FRCR, The Christie Hospital, The Christie NHS Foundation Trust, Wilmslow Rd, Manchester, M20 4BX, UK

⁶ Matthew Hatton, FRCR, Department of Clinical Oncology, Weston Park Hospital, Whitham Road, Sheffield, S10 2SJ, UK.

⁷ Jacqueline Clarke, FRCR, Cancer Centre, Belfast City Hospital, Lisburn Road, Belfast, County Antrim, BT9 7AB

⁸ Prof Ian H. Kunkler FRCR, Edinburgh Cancer Research Centre, Institute of Genetic and Molecular Medicine, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, UK.

⁹ Nicola S. Russell PhD, Department of Radiotherapy, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands.

Corresponding author - Galina Velikova PhD, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds Cancer Centre, St James's University Hospital, Beckett Street, Leeds, LS9 7TF, UK

g.velikova@leeds.ac.uk

Tel: +44 113 2067917

*Joint senior authors

Summary

Background Post-mastectomy radiotherapy (PMRT) in patients with 4+ axillary nodes reduces breast cancer mortality, but its role in patients with 1-3 involved nodes is controversial.

Methods BIG2-04-MRC-EORTC SUPREMO is an international parallel randomised controlled trial. Eligible women (over 18 years, with 'intermediate risk' breast cancer, pT1-2N1, pT3N0 and pT2N0 if grade III and/or lympho-vascular invasion, post-mastectomy and axillary surgery) were randomly assigned to receive chest-wall radiotherapy (50 Gy 25 fractions or radiobiologically equivalent 45 Gy 20 fractions or 40 Gy 15 fractions) or not (1:1 ratio). Randomisation was in permuted blocks with varying block length, stratified by centre, without masking of patients or investigators. The primary endpoint is 10-year overall survival. Here, we present the 2-year quality of life (QOL) results (pre-specified secondary endpoint). The QOL substudy, open to all UK patients, consists of questionnaires (EORTC QLQ-C30 and BR23, Body Image Scale, Hospital Anxiety and Depression Scale (HADS) and EQ-5D-3L) completed pre-randomisation, 1, 2, 5 and 10 years. Data were analysed on an intention-to-treat basis, using repeated mixed-effects methods. The trial is registered with International Standard Randomised Controlled Trials (ISRCTN61145589).

Findings

Between August 4, 2006-April 29, 2013, 1688 patients enrolled internationally, 989/1258 (79%) of the UK patients consented to QOL substudy. Patients receiving PMRT reported worse chest-wall symptoms ($p=0.016$) but the difference was small. Symptoms improved from year 1 to 2. Chemotherapy was associated with less improvement. No group differences were observed for arm symptoms, body image, fatigue, pain, overall QOL, physical functioning or HADS scores.

Interpretation PMRT led to more local symptoms up to 2 years post-randomisation, but the difference was small. This data will inform shared decision-making whilst survival results (main trial endpoint) become available.

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Research in Context

Evidence before this study

Adjuvant chest-wall irradiation after mastectomy remains a core effective element in the loco-regional management of early breast cancer reducing loco-regional recurrence and breast cancer mortality. While the evidence base for post-mastectomy radiotherapy (PMRT) in patients with 4 or more involved axillary nodes is robust, its role in 'intermediate' risk patients with 1-3 involved nodes is controversial and practices vary. The Oxford overview in 2014 shows an advantage in overall survival from PMRT in patients with 1-3 positive nodes. However, the generalisability to contemporary practice of historical trials with different standards of surgery, radiotherapy and systemic therapy remains uncertain. Benefits in survival needs to be balanced against risk of loco-regional and cardio-pulmonary toxicity, particularly in conjunction with potentially cardiotoxic anthracyclines and trastuzumab. The recent American Society of Clinical Oncology guidelines on the use of PMRT emphasizes the importance of evaluating the risk-benefit ratio, but the overview data is derived from patients treated several decades previously and only a limited number of small studies looked at patient-reported outcomes, such as symptoms and quality of life.

Added value of this study

Our study uniquely investigated the impact of adjuvant PMRT on quality of life in a randomised trial including a large, well characterised population of UK patients with 'intermediate-risk' breast cancer post-mastectomy. At 2 years PMRT was associated with worse self-reported local symptoms (pain, swelling, skin problems in the "area of the affected breast") in comparison with no radiotherapy, but the difference is small, unlikely to be of clinical significance and the symptoms improved over time. There were no differences in arm symptoms, body image, fatigue, pain, overall QOL, physical functioning anxiety or depression.

Implications of all the available evidence

The impact on PMRT on 10-year survival, the primary endpoint of the main SUPREMO trial, will not be known before 2023. In the meantime, both options of administering or omitting PMRT are legitimate for patients in the intermediate risk category (1-3 positive lymph nodes). Our data will inform shared decision-making (as recommended in the recent North American guidelines on PMRT) and put patients in a better position to make an informed value judgment on what they consider relevant for their situation given the data on the patient-reported symptoms and QOL domains presented in this report. Both physicians and patients may be helped when weighing up the individual estimates of possible benefits of radiotherapy against the impact of PMRT on toxicity and quality of life.

Introduction

Current multimodality treatment for breast cancer has improved survival rates.¹ Avoiding overtreatment and balancing the treatment burden against benefit has become an important research field. Examples of trials investigating selective omission of radiotherapy or chemotherapy have recently been reported.^{2,3} While the impact of mastectomy and chemotherapy on quality of life has been well documented the additional effect of adjuvant radiotherapy following mastectomy is unclear. Chest wall pain, fatigue, anxiety about recurrence and depressive symptoms can all hold back recovery and return to normal activities of daily living.⁴

Adjuvant chest wall irradiation after mastectomy remains a core and highly effective element in the loco-regional management of early breast cancer reducing loco-regional recurrence and breast cancer mortality. While the evidence base for post-mastectomy radiotherapy (PMRT) in patients with 4 or more involved axillary nodes is robust, its role in 'intermediate' risk patients with 1-3 involved nodes is controversial and practice and guidelines vary.⁵ The Oxford overview in 2014 shows an advantage in overall survival from PMRT which included at least the chest wall in the target volume in patients with both 1-3 and 4 or more positive nodes.⁶ However, the generalisability of historical trials with different standards of surgery, radiotherapy and systemic therapy remains uncertain, especially as contemporary survival rates are much higher than in the studies included in the overview. Potential benefits in survival needs to be balanced against risk of loco-regional and cardio-pulmonary toxicity, particularly in conjunction with potentially cardiotoxic anthracyclines and trastuzumab. A recent update by the American Society of Clinical Oncology on the use of post-mastectomy radiotherapy emphasises the importance of evaluating the risk-benefit ratio, particularly in patients with a low risk of local failure.⁷ The benefit of PMRT relies on estimates of recurrence risk, modulated by biological tumour characteristics, weighed against the negative impact of PMRT on the risks of late toxicity (e.g. cardiac toxicity from radiotherapy may be increased by the combination with systemic therapy).⁸ The data currently available on these modulating effects is derived from patients treated several decades previously.

Selective use of post-mastectomy radiotherapy is being evaluated in the BIG 2.04 MRC EORTC SUPREMO trial, which assesses the effects of adjuvant chest wall radiotherapy without axillary irradiation in patients with 'intermediate risk' early breast cancer who have undergone mastectomy and adequate systemic therapy following contemporary guidelines for all treatment modalities. This is the largest randomised trial to date to assess the role of PMRT in this subset of patients. The endpoints have been previously described.⁹ In brief, the primary endpoint of the trial is overall survival at 10 years. Secondary end points include various breast cancer recurrence endpoints, toxicity, acute and late morbidity (cardiac morbidity and mortality) and quality of life. Sub-studies include the TRANS-SUPREMO seeking molecular markers of radiosensitivity, a cardiac substudy, and for UK patients only Quality of Life (QOL) assessment and Health Economics evaluation. These sub-studies will provide an important high-quality evidence base on the balance of potential benefits and treatment burden, to support patients and health care professionals during shared decision-making.

The long-term impact of breast cancer and its treatment on everyday life has been identified as a critical knowledge gap and a key priority for breast cancer research¹⁰. For radiotherapy, there is a limited information on treatment impact. A small number of trials have investigated self-reported breast, arm, and shoulder symptoms, functional outcomes and quality of life after radiotherapy, predominantly in breast conserving therapy¹¹⁻¹³. Patients usually report transient and short-term effects of radiotherapy, with relatively limited effect on overall quality of life^{14,15}.

No comprehensive QOL data exists in patients having PMRT and only a few studies have compared patient-reported outcomes following breast-conserving surgery versus mastectomy with and without reconstruction. Recent introduction of oncoplastic surgical techniques is expected to have an impact on post-treatment morbidity and patient satisfaction with body image^{16,17}. There is a

dearth of level 1 evidence assessing the impact of adjuvant post-mastectomy radiotherapy on QOL of patients who have undergone reconstruction.

The SUPREMO QOL substudy aimed to examine the effects of PMRT on several primary QOL outcomes (global QOL, fatigue, physical function, chest wall, shoulder and arm symptoms, body image, anxiety and depression) at 1, 2, 5, and 10 years post treatment. Here we report the 2-year results. To our knowledge, this is the first study looking at the impact of adjuvant radiotherapy on QOL in a large randomised trial confined to patients treated by mastectomy for early breast cancer (including patients undergoing breast reconstruction).

Methods

Study design and Participants

SUPREMO was an open label parallel randomized trial. Patients provided written informed consent before enrolment. The full eligibility, exclusion criteria and trial procedures are described in the trial protocol provided in the supplementary web material and online (<http://www.supremo-trial.com/SUPREMO%20protocol%20version29.pdf>). Briefly, eligible patients were women aged 18 years or older if they had undergone mastectomy for unilateral breast cancer, and an axillary staging procedure with axillary lymph node dissection, if node positive. Patients with 'intermediate risk' breast cancer were eligible, defined as pT1-2N1, pT3N0 and pT2N0, if also grade III and/or with lympho-vascular invasion on histology. Patients needed to be fit for surgery, radiotherapy or adjuvant systemic therapy. Exclusion criteria included previous or concurrent malignancy (except non-melanomatous skin cancer and carcinoma in situ of the cervix), ductal carcinoma in situ, bilateral breast cancer, pregnancy at the time of radiotherapy treatment and male gender.

Eligible patients were randomly assigned to receive chest-wall radiotherapy or not (1:1 ratio). All patients had to receive adequate systemic therapy following contemporary guidelines depending on patient and tumour characteristics. If this included chemotherapy, treatment regimes containing at least 4 cycles of anthracyclines were recommended. Adjuvant trastuzumab was given according to local practice. In 2011 the eligibility criteria were widened, following a protocol amendment (version 29 August 30,2010) approved by the Ethics Committee, to include neo-adjuvant chemotherapy.

For patients randomized to chest wall radiotherapy, radiation was given after the chemotherapy (when given). Radiotherapy treatment consisted of chest wall radiation to a total dose of 50 Gy in 25 daily fractions of 2 Gy over 5 weeks. Other permitted radiobiologically equivalent schedules included 45 Gy in 20 fractions over 4 weeks, and 40 Gy in 15 fractions over 3 weeks. Guidelines on treatment planning and set up were given, and there was a radiotherapy quality assurance programme in the trial. The use of bolus was permitted and had to be pre-specified per centre. Axillary irradiation was not permitted, but medial peri-clavicular and/or internal mammary chain irradiation was permitted according to local policy of the centres. Boost radiation was not permitted. Surgery, systemic therapy and pathology were also subject to pre-specified quality assurance. Additional recorded data included cardiovascular risk factors, radiotherapy cardiac and lung exposure parameters, systemic therapy (type, doses, and dates) and any reconstructive surgery (type, immediate or delayed). Patients with gross protocol violations (e.g. margins involved or less than 1mm for invasive cancer or DCIS) will be removed before the final analysis of the main trial. A mammogram of the opposite breast, if appropriate, was recommended at least in alternate years for 10 years from the date of mastectomy. The primary endpoint of the trial, overall survival, is not centrally reviewed. Serious adverse events were to be reported if they occurred during radiotherapy or within 30 days of the last radiotherapy session (fraction) whether or not they were related to the randomised treatment. Any toxicity assessed as a grade 4 or 5 acute or late morbidity score had to be reported on a SAE/SUSAR form for the entire follow up period of the trial. Adverse events were reviewed by

the Data Monitoring and Ethical Committee meeting every 6 months (or as often as they considered appropriate). Monitoring (source data verification) is carried out by the Cancer Clinical Trials Team in Edinburgh on 10% of the patient data of the main trial with site visits allowed in the UK. Higher levels of monitoring will be performed, if requested by the Data Monitoring Committee, or if particular safety issues are identified by the investigators, the trial management group of the trial steering committee.

The study was approved by the Multi-Centre Research Ethics Committee, Edinburgh (MREC 05/50501/106) and local research and development offices. Patients provided written informed consent before enrolment and had additional options to consent to the sub-studies, including QOL substudy.

Randomisation and masking

Consenting patients were randomized post-operatively to either chest-wall radiotherapy or no chest-wall radiotherapy (1:1 ratio). Patients were randomised by permuted blocks with the block length being varied randomly to minimise the effect of entry bias. Stratification was by treatment centre due to possible between centre differences in the manner in which radiotherapy is given. There was no masking by patients or investigators. Randomisation was performed via a telephone call to The Information and Statistical Division (ISD) at National Services Scotland.

Procedures for QOL substudy

All patients eligible for SUPREMO from UK centres were invited to participate in the QOL study. Patients who provided informed consent completed a questionnaire booklet in the clinic before randomisation. Completed booklets were sent to the trial's office and subsequent questionnaires were posted to patients at 12 and 24 months by the trial's office. If the baseline questionnaire was not returned to the trial's office further questionnaires could not be sent, as patients' names and addresses were not available to the trial co-ordinator. Reminders were sent to the hospitals where baseline questionnaires were overdue. No reminders were sent to patients at 12 and 24 months.

QOL was assessed using several well-validated questionnaires.

EORTC QLQ-C30 (version 3-0) and the breast module QLQ-BR23 (version 1-0). The QLQ-C30 consists of 30 questions addressing 5 functional scales (cognitive, emotional, physical, social, and role), 9 symptom scales (appetite loss, constipation, diarrhoea, dyspnoea, fatigue, financial difficulties, insomnia, nausea and vomiting, and pain), and one Global Health Status/QOL scale¹⁸. The EORTC QLQ-BR23 focuses on breast cancer specific issues and includes 23 questions addressing 4 functional: body image, future perspective, sexual enjoyment, and sexual functioning and 4 symptom scales: arm symptoms (swelling in arm or hand, arm or shoulder pain, and difficulty raising the arm), breast/chest wall symptoms (pain, swelling, oversensitivity, and skin problems in the area of the affected breast), systemic therapy side-effects, and upset by hair loss¹⁹. All scores for the EORTC QLQ-C30 and EORTC QLQ-BR23 were transformed to a scale from 0 to 100. Higher scores on the functional scales and Global QOL represent a superior level of functioning and better QOL, whereas higher scores in the symptom scales or items represent worse symptoms.

The Body Image Scale (BIS) is a 10-item scale designed specifically for use with cancer patients to assess aspects of attractiveness, sexual attractiveness and feelings or satisfaction with appearance. Scores were graded 0-3 and summed to produce a single score, where a higher score indicated more problems (score range from 0 to 30)²⁰.

Hospital Anxiety and Depression Scale (HADS) is a 14-item instrument with two sub-scales for anxiety and depression²¹. Scores range from 0 to 21 on each scale, with higher scores indicating more distress. Scores above 11 suggest probable cases of anxiety or depressive illness, and scores

between 8 and 10 indicate borderline cases. A combined score of 19 or above is considered indicative of psychological distress.

EQ-5D-3L questionnaire measures health status across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Respondents specify whether they have no problems, some problems or severe problems within each domain, on the day of response. These EQ-5D-3L health states descriptions are converted into a single summary index (range from 0 to 1) by attaching a value to each of the levels in each dimension. As is standard practice, these values were obtained from a large UK population study using a choice-based method of valuation.²² The resulting summary score, or utility value, can then be used directly in the cost-utility analysis.

Outcomes

The primary endpoint of SUPREMO trial is 10-year overall survival. Quality of life is a secondary endpoint alongside chest-wall recurrence, regional recurrence, disease free survival, acute and late morbidity and cost-effectiveness. In the QOL substudy we pre-specified as primary outcomes global QOL, fatigue, physical function, chest wall symptoms, shoulder and arm symptoms, body image, anxiety and depression. Secondary outcomes are role, social, sexual functioning, pain and nausea/vomiting.

Statistical analysis

Sample size for the SUPREMO QOL study was considered as a problem of estimation rather than a significance testing. With 200 evaluable patients per group the proportion of patients exhibiting a particular side-effect or specified degree of morbidity in a QOL domain could be estimated with a standard error of 3.5% or less. The corresponding difference between the groups could be estimated with a standard error of 5% or less. However, as there is usually a significant attrition over time, in order to have sufficient numbers by 10 years a target of 800 patients was set. The total sample size of SUPREMO was reduced during the course of the trial, following a protocol amendment approved by the ethics committee, from 3500 to 1600 but this did not affect the QOL substudy sample.

When calculating QOL questionnaire or sub-scale scores, we followed official questionnaire guidelines on handling missing individual items. In general, if more than 50% of the items were missing, sub-scale scores were not calculated (missing); if less than 50% of items were missing, those were replaced by the mean of the answered items and a score was calculated. Where no guidance existed, that score was recorded as missing.

In order to maintain the Normality of the residuals, the difference from baseline to each subsequent questionnaire was calculated for each scale. Repeated analysis of covariance was conducted using PROC MIXED, to allow for observations that are missing at random. Time and treatment allocation interactions were tested for each scale but are to be reported only where statistically significant. Baseline scores were included in each model as a covariate. As the QOL study was not originally powered for hypothesis testing, p-values are only included for illustration. However, the treatment with radiotherapy was our primary outcome, and any results that have a p-value of ≤ 0.05 with this variable will be discussed. Due to the large number of models, clinical variables will only be discussed if they exceed the more conservative threshold value of 0.01.

The principal analysis modelled the change in score in the pre-specified QOL outcomes (global QOL, fatigue, physical function, chest wall, shoulder and arm symptoms, body image, anxiety and depression) by time (visit 1 at 12 months or 2 at 24 months) of follow up, age group (<45, 45-54, 55-69, ≥ 70), baseline score and treatment (\pm radiotherapy).

As almost all patients received some form of systemic therapy and some underwent breast reconstructive surgery, secondary exploratory analyses were performed to evaluate whether these

treatments influenced the QOL outcome measures. The secondary analysis included clinical covariates also considered to have an impact on QOL (extent of axillary surgery, early breast reconstruction, adjuvant chemotherapy, adjuvant hormonal therapy and trastuzumab). This was performed by creating a basic model of age group, time and baseline score, then adding the clinical variables in turn to create a model of best fit. This process was then repeated until no variables added significantly to the model. The radiotherapy variable was then added to the best fit model. Only patients with complete data for all clinical variables were included in this modelling.

All analyses were on an intention to treat basis. No additional sensitivity analyses or interim analyses were planned for this stage of the trial. The analysis was generated using version 9.4 of the SAS System for Windows (www.sas.com Copyright © 2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.)

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN61145589.

Role of Funding Source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and the joint senior authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between August 4, 2006 and April 29, 2013 the trial recruited 1688 patients internationally. All patients eligible for SUPREMO from 111 UK centres were invited to participate in the QOL substudy (n=1258). This approach was adopted in order to avoid any bias in selecting centres or patients. The consent rate between centres varied (see Table consent rates in the web appendix, page 1). The majority of the centres (73 centres) had consent rates of 80% or above. Ten centres did not include any of their 66 patients in the QOL study. A total of 989 (79%) UK patients consented to participate, of them 95.7% (947/989) patients (returned the baseline questionnaires (476/502 94.8% in the control and 471/487 96.7% in the radiotherapy arm). The statistical analysis is based on 947 patients who returned the baseline QOL questionnaires (Figure 1). Due to the practical arrangements for the QOL data collection, questionnaires for years 1 and 2 could be sent only to patients who returned the baseline questionnaire. We have not formally recorded reasons for declining participation as according to the Ethics Committee approved patient information sheet, patients were not obliged to provide such reasons. The patients from UK who declined participation or did not return the baseline questionnaires were older (n=311 mean age 57.7 years, SD 11.9) than those who consented and returned the baseline questionnaire (n=947 mean age 56.1 years, SD=11.0; p=0.02). Comparing the age of QOL study participants with the rest of the main trial (UK patients not participating in QOL study and all patients from other countries) did not show an age difference (n=741 mean age 55.6 years, SD 11.6, p=0.34). In order to check further for potential bias in patient selection for the QOL substudy, we compared the clinical characteristics of the patients completing the QOL substudy with those of the patients in the main trial in Table 1.

Good patient compliance was achieved with the completion of QOL measures: at year 1 388/466 83.3% in the control group and 388/467 83.1% in the radiotherapy group; at year 2 (350/463 75.6% and 367/457 80.3% respectively. A slightly better compliance was observed in the radiotherapy arm at baseline and year 2 (Figure 1).

Median follow-up for the patients who returned the baseline questionnaires was 748 days (interquartile range 417-763) for the control group and 749 days (interquartile range 725-762) for radiotherapy group.

Patient characteristics

Patients' demographic, clinico-pathological characteristics and treatment details are shown in Table 1. There is good balance in clinical characteristics between the radiotherapy and no radiotherapy groups in the QOL substudy. Some 70% (669/947) of patients had T2 tumours, 54% (512/947) were Grade 3, 78% (746/947) were ductal carcinomas, 19% (180/947) were oestrogen/progesterone receptor negative, and 30% (285/947) Her2 positive. Only a small proportion of 11% (11/947) had immediate reconstruction, and 11% (106/947) late reconstruction (by 2 years). A further review of the type of breast reconstruction suggested more frequent autologous reconstructions in the radiotherapy group, whereas there were more reconstructions with an implant/expander in the control group (see Web appendix, page 2). This trend was observed for both the immediate and the late reconstructions. Some 84% (796/947) of participants had adjuvant chemotherapy, 19% (183/947) trastuzumab and 75% (712/947) endocrine therapy. No differences are observed between the QOL participants and the full trial.

The majority of patients in the radiotherapy group of the QOL study received 40 Gy in 15 fractions (69%, 327/478), with the remaining patients equally divided between 50 Gy in 25 fractions (11%, 52/478), 45 Gy in 20 fractions (10%, 48/478) and other/unknown (10%, 51/478). In the main trial, a smaller proportion of 52% (445/853) received 40 Gy in 15 fractions, a larger proportion of 27% (227/853) had 50 Gy in 25 fractions, 7% (57/853) had 45 Gy in 20 fractions and 15% (124/853) - other/unknown. The dose for all EORTC centres was 50 Gy in 25 fractions.

Baseline and follow-up QOL scores are shown in Table 2. Baseline scores were reported following surgery and prior to randomisation. Of note, patients reported relative impairment in global QOL with a mean score of 60 (100 is excellent), a high level of fatigue (mean of 40, where 100 is greatest degree of fatigue), insomnia (mean of 36-37; 100 is worse) and a degree of arm symptoms, chest wall symptoms and pain (in the range of 17 to 24; 100 is worst symptom).

Pre-specified primary QOL outcomes

Table 3 presents the results from mixed-effects models analysis of pre-specified primary QOL outcomes and pain (a pre-specified secondary QOL outcome). The tested clinical variables are included in Table 3 where they were found to have a significant effect ($p < 0.01$) on either the radiotherapy treatment or on changes over time. Such effects were found for adjuvant chemotherapy and immediate breast reconstruction but not for extent of axillary surgery, adjuvant endocrine therapy or trastuzumab.

Chest wall symptoms were worse in the group receiving radiotherapy (estimate of effect 2.17; 95% Confidence Interval (CI) 0.40, 3.94; $p = 0.016$). There was an improvement between years 1 and 2 (visit effect -1.34; 95% CI -2.36, -0.31; $p = 0.010$), but the improvement was smaller in the radiotherapy group (Figure 2a). Of the clinical factors the use of chemotherapy was associated with less improvement in chest wall symptoms but there was no interaction with radiotherapy, suggesting an additive effect of chemotherapy (Figure 2a). There was a borderline age effect, with patients <45 years having worse chest-wall symptoms than those ≥ 70 years (estimate of effect 4.49; 95% CI 0.59, 8.39; $p = 0.022$).

Arm problems did not differ significantly according to radiotherapy treatment (Figure 2b), they improved in both group between years 1 and 2, with a greater improvement in older patients (data not shown). When clinical variables were included the effect of age was no longer apparent. However, chemotherapy had an effect with patients receiving chemotherapy showing less improvement of arm symptoms over time, suggesting that chemotherapy and age were confounders. Significantly more patients who received chemotherapy were in the younger age group (97% of patients <45 years, 97% in 45-54 years, 85% in 55-69 years, 37% in ≥ 70 years groups, $P <$

0.0001). Contrary to the clinical expectations, the extent of axillary surgery (comparison of 3 types: 1) sentinel node biopsy or node sampling; 2) sentinel node biopsy plus axillary node clearance; 3) axillary node clearance) did not have an effect on arm/shoulder symptoms scores (see Web appendix, page 3). Furthermore, the extent of axillary surgery did not have an impact on any of the pre-specified QOL variables, except a trend for higher HADS-Anxiety in patients with sentinel node biopsy plus axillary node clearance.

Despite the observed differences in chest-wall symptoms patients reported relatively few body image problems with improvement between years 1 and 2. Some age effect was observed with patients <45 years old reporting more concerns about their body image in comparison with patients ≥70 years old (estimate of effect 1.96; 95% CI 0.53, 3.39; $p=0.0074$).

The overall QOL of patients was not affected by radiotherapy treatment. Furthermore, improvement in overall quality of life was observed between baseline and year 1 with further but smaller improvement by year 2 (Figure 2c).

Physical function was not affected by treatment and no change was observed over time (Figure 2d). As expected there was an age effect with the younger age group reporting better overall physical functioning (Table 3).

Patients reported high baseline level of fatigue, likely due to the preceding surgery. Significant improvement between year 1 and 2 was observed. Immediate reconstruction had a borderline impact on the change scores at year 1 (estimate of effect 5.32; 95% CI 0.94, 9.69; $p=0.017$), possibly related to slower recovery from the operation (Figure 2e), but without detectable differences in overall QOL or body image.

No group differences were seen in HADS-Anxiety and HADS-Depressions scores. Women younger than 70 reported higher levels of Anxiety with improvement from baseline to year 1 and to year 2 in both groups.

Pre-specified secondary QOL outcomes

An interesting pattern in self-reporting of general pain was observed. The mean score at baseline was just over 20 in both groups, but without any improvement from baseline to year 1 or year 2 independent of randomisation arm, which is at odds with some of the findings for the primary outcomes (global QOL, fatigue, chest-wall symptoms, body image and anxiety) where we observed an improvement from baseline. We investigated the potential impact of systemic treatments. Borderline effects were found for use of trastuzumab ($P=0.06$) and chemotherapy ($P=0.08$), possibly associated with the use of taxanes. No effect was found for endocrine therapy (none vs tamoxifen vs aromatase inhibitors).

No between-group differences were observed for nausea/vomiting, sexual, role and social functions. Gradual improvement over time was observed without any effect of treatments. Role function and social function showing the biggest numerical improvement over time, in year 1 with continued improvement in year 2. Patients having radiotherapy reported larger improvements in their social function in comparison with those who did not. Patients reported very low scores on sexual functioning (mean of 11 out of 100). We had good completion rate for the general sexual function questions 97% (914/947) but only 27% (253/914) patients completed the conditional sexual enjoyment questions at baseline suggesting that the vast majority of patients are not sexually active (Table2). These observations are consistent with other reports.

The exploratory analysis of the other scales is in the web appendix page 5. All remaining scales and items did not show any impact of radiotherapy treatment and all show improvement or stability over time.

Discussion

To our knowledge, this is the first study investigating the impact of adjuvant radiotherapy on quality of life after mastectomy in a large randomised trial including a substantial, well characterised population of UK patients with 'intermediate-risk' breast cancer. The key finding is that PMRT was associated with worse local self-reported symptoms (pain, swelling, oversensitivity and skin problems in the "area of the affected breast") in comparison with no radiotherapy, although these symptoms improved over time. The estimated effect is small, with a difference in 'change scores' between the radiotherapy and control group of 2.17 points; 95% CI 0.40, 3.94. There is published data on EORTC QLQ-C30 on 'change scores' within groups or 'scores difference' between groups that is clinically significant, but to the best of our knowledge, there is no such available data on EORTC-BR23 scores²³. We opted to present the mean scores and standard deviations in order to allow comparisons with other studies. In an attempt to explore the clinical significance of the observed statistically significant difference, we looked at using a generic approach of 0.5 of the standard deviation to indicate minimally important difference. Therefore, we calculated the standard deviation of the 'change score' for chest wall symptoms from baseline to year 1 in the control group.²⁴ The standard deviation was 17.3 and a score 8.65 is likely to indicate a clinically meaningful difference. The observed difference of 2.17 is relatively small and unlikely to be of clinical significance, which is of course reassuring for patients and clinicians. Recent guidelines from Federal Drugs Administration (FDA) recommend establishing a meaningful change in patient reported outcome measures at the individual level (i.e., defining a responder) versus at the treatment group level²⁵. The definition of a responder being "a score change in a measure, experienced by an individual patient over a predetermined time period that has been demonstrated in the target population to have a significant treatment benefit". Using this approach and a 'change score' of 8.65 as a cut-off score for clinical significance we applied 'responder analysis' (web appendix page 7). We calculated proportions of patients whose scores 'improved' by < -8.65 points between baseline and year 1, those who remained 'stable'/no change' (change score= ± 8.65) and those whose scores 'worsened' by $> +8.65$ points. This 'responder analyses' showed that 16.3% (63/386) of patients receiving radiotherapy reported clinically meaningful worse 'change score' vs 11.9% (46/385) of those without radiotherapy. In other words, 4.4% more patients on radiotherapy experience worse chest wall symptoms than those not receiving PMRT. This way of interpretation of results may be more informative to clinicians and patients, but a note of caution is appropriate due to the assumptions described above.

There was no impact of radiotherapy to the chest wall on arm symptoms (axillary radiotherapy was prohibited in the trial), body image, overall QOL, physical function, fatigue or symptoms of anxiety or depression. Exploratory analyses showed that systemic chemotherapy treatment had an additive borderline effect on patients' chest wall and arms symptoms but without an interaction with the radiotherapy treatment. This is consistent with other studies²⁶.

Sentinel node biopsy procedure is the current standard surgical staging procedure for the axilla. In SUPREMO about a quarter of patients (those with pN0 (sn) tumours) in the main and QoL substudy underwent limited axillary surgery (sentinel node biopsy or nodal sampling). The extent of axillary surgery had no impact on any of the pre-specified QOL outcomes, including arm symptoms. This is perhaps an unexpected finding and could be due to lack of sensitivity of the EORTC BR23 scale (which has 3 items on 'pain in arm or shoulder', 'swollen arm or hand' and 'difficulty raising your arm'). The impact of radiotherapy to the axilla on arm symptoms cannot be evaluated in the SUPREMO trial, as this was prohibited. Our findings are not generalisable to women who were treated with both an axillary nodal dissection and regional nodal radiotherapy. This treatment is generally reserved for patients with higher nodal load (N2 and N3 disease) than included in the SUPREMO trial (pN0 or pN1).

Neo-adjuvant treatment was allowed in a later protocol version (version 29), but the number of treated patients is too small (n=8) for valid conclusions and therefore we did not perform any between group comparisons.

We observed a low rate of immediate breast reconstruction (only 111 patients). This procedure was associated with higher fatigue levels and slower recovery in comparison with no immediate reconstruction but no impact on body image or the other QOL outcomes. The estimated effect of immediate reconstruction on fatigue was 5.32, corresponding to a small clinically meaningful difference²³. This was an exploratory analysis and we used a generic QOL and body image questionnaires rather than breast-reconstruction instruments (such as BREAST-Q), which is likely less sensitive to specific outcomes¹⁷.

The observed low levels (11%) of reconstructive surgery (either immediate or delayed to year 2) should be noted. This likely reflects the pattern of care in the period of the SUPREMO trial recruitment (2006-2013) or may be due to concerns of entering patients who had reconstruction into a trial of radiotherapy. There appears to be a trend in using more autologous procedures in patients who had radiotherapy and more implants/expanders in those not receiving radiotherapy. Due to the small number of reconstructions, SUPREMO trial cannot provide useful information on the impact of radiotherapy on breast reconstruction. We are collecting further information on delayed (beyond 2 years) reconstructions, which will be analysed at 5 and 10 years and provide valuable information on rates of breast reconstruction across the UK, as well as its impact on patients' experiences and satisfaction with body image. Furthermore we do not have the power to assess between group differences taking into account the dose schedules in the radiotherapy group. A direct comparison of conventional versus hypo-fractionation for chest wall radiotherapy after breast reconstruction is being carried out in North America by the Alliance for Clinical Trials in Oncology (NCT03414970). The primary objective is to evaluate whether the reconstruction complication rate at 24 months post radiation is non-inferior with hypofractionation. The trial is ongoing and will complete recruitment in 2021, with final results in August 2025.

Most of the published literature relating to the impact of adjuvant radiotherapy on QOL relates to non-randomised studies, often of small size, which may be subject to selection bias and neither surgery, radiotherapy nor were systemic treatments subject to pre-specified quality assurance. Comparisons are often difficult because of differing types of surgery, stage of disease, QOL measures used and time-points of QOL assessment. Studies often included both patients treated by mastectomy and breast conserving surgery. The START trial looked at late effects of different schedules of radiotherapy at 5 years and found that up to a third of women reported moderate or marked pain in the arm and shoulder and more than 10% experienced arm/hand swelling¹². The trial included a small number of mastectomy patients (about 20%) and although the QOL results are consistent with ours, they are not directly comparable since only 10% had chemotherapy and 20% had regional nodal irradiation in addition to breast/chest wall radiotherapy. The experience of breast/arm symptoms over 5 years represents chronic morbidity that has stronger association than cosmesis with long-term quality of life, making these important outcomes in clinical trials²⁷.

The Moving Beyond Cancer psychosocial intervention trial studied the QOL of 558 women with stage 1 and 2 breast cancer treated with surgery alone (breast conserving or mastectomy), surgery with radiation, or surgery followed by chemotherapy and radiation over 1 year, using SF-36 questionnaire. Similar to our study, physical and psychosocial function improved significantly over time. However, the measures of QOL differ from our study and details of chemotherapy regimes and staging were not available in the absence of case record review²⁶. A similar pattern of improvement in a range of symptoms and QOL measures in the first year post diagnosis was observed in a cohort study of 285 women with early breast cancer, treated with surgery (just >20% had mastectomy), adjuvant radiotherapy (74%) and systemic therapy in (just >30% of the patients)²⁸.

Finally, we observed that younger women reported worse body image (if under 45) and anxiety problems (if under 70 years). This finding is supported by other breast cancer QOL studies, is concordant with clinical experience and emphasises the need for targeted psychological interventions in those women^{11,29}. Younger women also reported higher general pain scores which

did not improve with time, and this was not related to the use of aromatase inhibitors (data not shown). The reasons for this are not clear. Persistent pain following breast surgery (breast conserving or mastectomy) was reported by half of the patients in a population-based prospective study of over 3000 patients. The pain was commoner after adjuvant radiotherapy and in younger women.³⁰ The same finding was also reported in a randomised trial of radiotherapy after breast conserving therapy^{13,30}. The wide variation in reports (25% -60%) may relate to varying definitions of pain, different methods of pain assessment and mix of surgery and adjuvant therapy. There is insufficient evidence to draw conclusions on each of the treatment-related risk factors for pain.

Several strengths of SUPREMO QOL substudy should be mentioned. It is the largest post-mastectomy study which is investigating a well-defined large population of patients treated by mastectomy, which was representative of women with early 'intermediate-risk' breast cancer in the UK. Individuals in the QOL study were recruited from almost all UK sites. Only 10 out of 111 sites did not recruit any of their 66 patients, a relatively small number of centres and unlikely to have an impact. We do not know the reasons for the low consent rates in some centres, but it may be related to availability of local resources (dedicated clinical research nurses). This was a large pragmatic study and resources were not available to monitor closely consent rates by centre or to provide extra support.

The QOL study was multi-centre from across the UK, representing a wide geographical range, thus minimising participating centre bias. The pre-specified QOL sample size was achieved and exceeded, strengthening our confidence in the findings. The trial was sufficiently large to allow explorative evaluation of the effects of age and multi-modality treatments. High levels of adherence to questionnaire completion over time were attained (>70%). In addition, guidelines on surgery, radiotherapy and systemic therapy were standardised in the protocol, so any variations in these treatment modalities between treatment arms are unlikely to influence the results.

The main limitation of the QOL substudy is not having a true pre-treatment baseline QOL assessment, as all patients were randomised following mastectomy. The relatively low QOL scores at the time of randomisation may be explained by the recent breast cancer diagnosis and the surgical procedure, and the subsequent improvement in almost all scores, is to be expected. We did not record QOL scores during or shortly after the allocated radiotherapy treatment, so any differences in acute symptoms between the groups, which may predict later toxicity, have not been captured. In addition, since the main trial is ongoing and the loco-regional control and survival status of the patients in the QoL substudy are not known to us, it is possible patients who had relapsed or died may have had different patterns of QOL.

A larger proportion of participants in the QOL study received the dose fractionation schedule as 40 Gy in 15 fractions (69%) compared to 52% in the main trial, where a larger proportion of 27% received 50 Gy in 25 fractions. This difference reflects the variations between the standard practice in UK and EORTC centres at the time of the trial.

At this 2-year analysis we have not evaluated any effect of fractionation on the QOL outcomes. However, as the clinical significance of the increased chest wall symptoms in the radiotherapy group at 2 years may be relatively limited, we do not expect a major clinical impact of fractionation at this early time point. We expect that the difference in symptoms reported by patients between no radiotherapy and 40-50 Gy will be larger than any difference observed between fractionation schedules. The influence of radiation dose fractionation and technique and the radiation dose parameters to organs at risk will be the subject of a more detailed analysis to be performed in the irradiated group, including evaluation of toxicity (physician scoring). The results will be reported in a separate publication, focusing on the specific technical aspects of the radiotherapy.

This paper presents a pre-planned analysis at 2 years post randomisation, with the main QOL analysis being planned at 5 years and QOL data to be collected for 10 years to capture late adverse events. Clearly our results are preliminary and we are therefore cautious in our interpretation.

However, it is reassuring that the loco-regional symptoms are minimal and do not impair global QOL and diminish over the initial 2 years of follow up. While it might be argued that analysing QOL at 2 years is too premature, this was a pre-planned analysis. We considered it appropriate to identify any potential early signals of a significant impact on QOL in the absence of a definite oncological outcome. If severe QoL effects were to be identified early, then this would be relevant for clinical decision making in the absence of information on long-term survival benefit. The recent North American guidelines on post mastectomy radiotherapy⁷ emphasise the importance of shared decision making between physician and patient in weighing up the benefits and toxicity of treatment in patients with 1- 3 positive node undergoing axillary node clearance. Information on the impact of PMRT on QOL may help inform this decision-making process, even before the main trial outcomes become available. Further analyses will be reported at 5 and 10 years to determine if the trends at 2 years are sustained. It is possible that late radiotherapy toxicity not seen within the first two years (such as progressive chest wall fibrosis or increased cardiac toxicity due to the combination of radiotherapy and anthracycline-based chemotherapy) may be detected on longer term follow-up and should be captured in our 5 and 10 year analyses. However, we recognise that late cardiac toxicity from radiotherapy may occur beyond 10 years.

The impact on PMRT on 10-year survival, the primary end-point of the main SUPREMO trial, will not be known before 2023. In the meantime, the decision to administer or omit PMRT can be considered 'preference sensitive' for patients in the SUPREMO trial risk category of 1-3 positive lymph nodes, as both options are legitimate. The patients will be in a better position to make a value judgment on what they consider relevant for them, given the data on various QOL domains presented in this report. Both physicians and patients may thus be helped when weighing up the individual estimates of possible benefits of radiotherapy against the impact of PMRT on toxicity and QOL endpoints.

In conclusion, chest wall radiotherapy led to more chest wall symptoms up to 2 years post-randomisation, but the difference is small and unlikely to be clinically significant. There was no impact on the other pre-specified QOL domains. However, the trend for worse QOL scores for anxiety, body image and chest-wall symptoms in younger women irrespective of irradiation warrants further investigation. Longer term follow-up at 5 and 10 years will be needed to see if these early trends in quality of life are sustained.

Contributors

GV LW SW JMD IHK NSR were involved in the study design. IHK NSR oversaw the trial and GV LW SW JMD were members of the trial management group. JMD JL MH JC IHK NSR recruited patients. LW GV SW IHK NSR did the data analysis. GV SW JMD JL MH JC IHK NSR interpreted the data. GV LW SW IHK NSR wrote the paper. JMD JL MH JC reviewed the drafts. GV IHK NSR gave final approval of the manuscript.

Declarations of interest

GV has received research grants from National Institute of Health Research (NIHR), Cancer Research UK, Yorkshire Cancer Research and personal fees from Roche, Novartis, and Eisai. SW has received research grant from NIHR. JMD has received personal fees from Pfizer. IHK has received research funding from NIHR. NSR has received research grants from the Dutch Cancer Society and EORTC. The other authors declare no competing interests.

Acknowledgments

We thank the patients, their relatives and treating clinicians, and the hospitals who agreed to participate in this study. The list of contributors from UK participating centres is provided in an online appendix.

We thank Medical Research Council (MRC)(EME 09/800/31), European Organisation for Research and Treatment of Cancer (EORTC), Cancer Australia, The Dutch Cancer Society, the Trustees of the Hong Kong and Shanghai Banking Corporation (HSBC) for funding the study.

We wish to acknowledge the support of the staff at The Information and Statistical Division at National Services Scotland and specifically Kathleen Riddle Principal Trial Manager, Penny Hopwood (The Christie Hospital, Manchester) initial chief Investigator for the QOL substudy (who has subsequently retired), the Scottish Cancer Trials Breast Group under whose auspices the trial was run (Chair: Dr Iain MacPherson), the Trial Management Group, the Trial Steering Committee (Chair Professor Barry Hancock, University of Sheffield), and the Data Monitoring and Ethical Committee (Chair Professor Chris Frost, London School of Hygiene and Tropical Medicine).

We also thank the National Institute for Health Research Cancer Research Networks in England and their equivalent NHS R&D-funded networks in Scotland, Wales, and Northern Ireland for “in-kind” support.

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Tables

Table 1. Patients' demographic and clinical characteristics

Patient demographic and clinical characteristics	QOL study		Full trial	
	No RT	RT	No RT	RT
Demographic	476	471	835	853
Age (mean and SD)	56.3 (11.3)	55.8 (10.8)	55.9 (11.2)	55.8 (11.3)
Menopausal status (number, %)				
Pre-menopausal	126 (26.5)	135 (28.7)	246 (29.5)	243 (28.5)
Peri-menopausal	43 (9.0)	52 (11.0)	68 (8.1)	85 (10.0)
Post-menopausal	290 (60.9)	268 (56.9)	483 (57.8)	475 (55.7)
Not known	17 (3.6)	16 (3.4)	38 (4.6)	50 (5.9)
Tumour characteristics				
Side of primary tumour (number, %)				
Left	238 (51.2)	216 (47.8)	398 (50.1)	407 (51.3)
Right	227 (48.8)	236 (52.2)	396 (49.9)	387 (48.7)
Tumour size (number, %)				
≤2cm	132 (27.7)	138 (29.3)	249 (29.8)	261 (30.6)
2.1-5 cm	337 (70.8)	332 (70.5)	566 (67.8)	566 (66.4)
>5 cm	5 (1.1)	1 (0.2)	4 (0.5)	4 (0.5)
Unknown	2 (0.4)	0	16 (1.9)	22 (2.6)
Tumour grade (number, %)				
I	20 (4.2)	23 (4.9)	46 (5.5)	57 (6.7)
II	190 (39.9)	195 (41.4)	335 (40.1)	333 (39.0)
III	262 (55.0)	250 (53.1)	432 (51.7)	432 (50.6)
Not specified	4 (0.8)	3 (0.6)	22 (2.6)	31 (3.6)
Histological type (number, %)				
Ductal	372 (78.5)	374 (79.4)	641 (78.2)	661 (79.5)
Lobular	58 (12.2)	49 (10.4)	95 (11.6)	89 (10.7)
Mucinous	5 (1.1)	1 (0.2)	7 (0.9)	1 (0.1)
Tubular	1 (0.2)	3 (0.6)	4 (0.5)	4 (0.5)
Adenocarcinoma	3 (0.6)	5 (1.1)	16 (2.0)	13 (1.6)
Other	35 (7.4)	39 (8.3)	57 (7.0)	63 (7.6)
Molecular markers – (number, %)				
ER+/PR+	218 (46.8)	217 (46.7)	417 (51.5)	416 (50.6)
ER+/PR-	48 (10.3)	48 (10.3)	83 (10.3)	99 (12.0)
ER-/PR+	5 (1.1)	0 (0)	8 (1.0)	3 (0.4)
ER-/PR-	87 (18.7)	93 (20.0)	156 (19.3)	162 (19.7)
ER+/PR unknown	96 (20.6)	100 (21.5)	131 (16.2)	132 (16.0)
ER-/PR unknown	12 (2.6)	7 (1.5)	15 (1.9)	11 (1.3)
Her2 positive	140 (29.7)	145(31.1)	273 (33.5)	269 (32.5)
Her2 negative	286 (60.7)	281 (60.2)	475 (58.2)	469 (59.9)
Not measured	45 (9.6)	41 (8.8)	68 (8.3)	63 (7.6)

Patient demographic and clinical characteristics	QOL study		Full trial	
	No RT	RT	No RT	RT
Axillary Nodes (number, %)				
0 (negative)	130 (27·3)	113 (24·0)	219 (26·2)	212 (24·9)
1-	180 (37·8)	199 (42·3)	316 (37·8)	338 (39·6)
2-	101 (21·2)	111 (23·6)	178 (21·3)	194 (22·7)
3-	63(13·4)	48 (10·2)	107 (12·8)	88 (10·3)
Not known	2 (0·4)	0	15 (1·8)	21 (2·5)
Treatment				
Breast Surgery (number, %)				
Mastectomy only	371 (77·9)	359 (76·2)	653 (78·2)	669 (78·4)
Immediate breast reconstruction prior to RT	50 (10·5)	61 (13·0)	85 (10·2)	97 (11·4)
Late breast reconstruction	55 (11·6)	51 (10·8)	97 (11·6)	87 (10·2)
Axillary surgery (number, %)				
SLN / node sampling	131 (27·9)	108 (22·9)	207 (25·5)	189 (22·8)
SLN plus ANC (Axillary node clearance)	138 (29·4)	124 (26·3)	229 (28·2)	224 (27·0)
ANC (without SLN)	201 (42·8)	239 (50·7)	377 (46·4)	417 (50·2)
Systemic treatment (number Yes, %)				
Neo-adjuvant chemotherapy ¹	1/173 (0·58)	7/173 (4·1)	7/243 (2·9)	16/269 (6·0)
Adjuvant chemotherapy	395/476(83·0)	401/471(85·1)	682/835(81·7)	709/853(83·1)
Anthracyclines	372/395(94·2)	379/401(94·5)	636/682(93·3)	655/709(92·4)
Taxanes	197/395(49·9)	207/401(51·6)	392/682(57·5)	418/709(59·0)
Trastuzumab	91/454 (20·5)	92/460 (20·0)	150/782(19·2)	166/806(20·6)
Endocrine therapy (number Yes, %)				
Neo-adjuvant	2/200 (1·0)	8/206 (3·9)	10/288 (3·5)	17/316 (5·4)
Adjuvant	349 (73·3)	363 (77·1)	598 (71·6)	631 (73·9)
Aromatase inhibitor	173/349(49·6)	195/363(53·7)	275/598(46·0)	314/631(49·8)
Tamoxifen	174/349(49·9)	168/363(46·3)	319/598(53·3)	314/631(49·8)
Other	2/349 (0·6)	0/363 (0)	4/598 (0·8)	3/631 (0·5)

¹ Only recorded in protocol v29 onwards; the denominator is the total number of recorded chemotherapy treatments from protocol v29 onwards

ER- estrogen receptor; PR – progesteron receptor; SLN- sentinel lymph node(s) procedure; ANC – axillary node clearance

Table 2. Quality of Life (QOL) scores (Standard Deviations, SD) at baseline, year 1 and year 2 follow-up

QoL measure	Baseline		Year 1		Year 2	
Mean (SD)	No RT (n=476)	RT (n=471)	No RT (n=388)	RT (n=388)	No RT (n=350)	RT (n=367)
Age at randomisation	56.3 (11.3)	55.8 (10.8)	56.5 (10.9)	56.1 (10.4)	56.8 (10.9)	56.1 (10.4)
Primary endpoints						
<i>EORTC QLQ-C30</i>						
Global Health/QOL*	60.9 (21.6)	60.4 (20.8)	70.0 (20.5)	70.0 (19.8)	70.2 (20.5)	71.8 (20.1)
Fatigue**	41.6 (25.2)	43.0 (26.1)	30.3 (23.2)	31.0 (24.1)	29.2 (24.2)	27.5 (23.8)
Physical Functioning*	79.6 (20.2)	80.1 (19.6)	81.9 (19.0)	81.1 (19.1)	82.0 (18.6)	82.1 (19.3)
<i>EORTC QLQ-BR23</i>						
Arm symptoms**	20.3 (20.5)	21.2 (21.7)	21.2 (21.7)	22.4 (22.0)	20.7 (21.4)	19.9 (20.3)
Chest wall/breast symptoms**	17.3 (17.0)	18.1 (18.3)	13.1 (16.3)	16.1 (16.7)	11.6 (14.6)	14.1 (15.8)
<i>Body Image Scale**</i>	10.3 (7.9)	11.1 (8.2)	9.3 (7.6)	9.8 (7.7)	8.1 (6.7)	8.7 (7.4)
<i>Hospital Anxiety and Depression Scale (HADS)</i>						
Anxiety	6.2 (4.4)	6.1 (4.3)	6.8 (4.7)	6.5 (4.4)	6.3 (4.3)	6.5 (4.4)
Depression	4.5 (3.7)	4.6 (3.7)	4.2 (3.7)	4.2 (3.8)	4.0 (3.5)	4.2 (3.9)
Secondary endpoints						
<i>EORTC QLQ-C30</i>						
Role Functioning *	65.2 (30.9)	63.0 (30.5)	79.3 (27.1)	78.8 (25.8)	79.7 (27.6)	81.0 (26.9)
Social Functioning *	65.5 (28.7)	64.0 (29.1)	79.4 (25.6)	80.3 (24.7)	80.5 (26.1)	83.9 (25.2)
Pain**	22.6 (26.5)	24.8 (27.9)	21.7 (26.8)	23.7 (26.5)	23.4 (27.3)	21.6 (25.9)
Nausea Vomiting**	11.2 (17.6)	11.5 (20.1)	5.3 (13.1)	5.1 (12.1)	4.6 (12.2)	5.1 (13.6)
<i>EORTC QLQ-BR23</i>						
Sexual Functioning*	11.5 (18.1) n=455	12.5 (19.0) n=459	15.7 (20.5) n=372	17.6 (21.2) n=374	16.3 (21.7) n=325	18.1 (22.3) n=353
Exploratory variables						
<i>EORTC QLQ-C30</i>						
Emotional Functioning*	74.7 (22.6)	73.7 (24.4)	75.2 (23.6)	75.2 (22.3)	77.3 (22.5)	75.7 (23.3)
Cognitive Functioning*	77.1 (23.4)	75.0 (26.1)	78.2 (22.8)	78.2 (22.9)	78.6 (22.8)	78.2 (23.8)
Dyspnoea**	20.8 (26.4)	20.0 (26.1)	14.6 (23.5)	14.8 (23.0)	14.3 (23.2)	13.4 (22.5)

QoL measure	Baseline		Year 1		Year 2	
Mean (SD)	No RT (n=476)	RT (n=471)	No RT (n=388)	RT (n=388)	No RT (n=350)	RT (n=367)
Insomnia**	36.3 (31.1)	37.2 (32.8)	36.4 (33.5)	38.5 (32.8)	33.9 (31.9)	35.0 (30.5)
Appetite loss**	20.7 (28.9)	19.2 (27.9)	9.5 (19.8)	8.7 (18.5)	9.1 (19.9)	9.0 (20.7)
Constipation**	18.2 (26.3)	17.0 (26.1)	14.9 (24.5)	14.5 (24.1)	17.6 (27.7)	14.5 (24.3)
Diarrhoea**	11.9 (20.7)	12.1 (23.8)	7.6 (17.5)	8.4 (18.7)	5.4 (15.1)	8.7 (19.1)
Financial difficulties**	23.9 (33.1)	23.2 (31.7)	15.8 (28.5)	17.1 (27.8)	14.1 (27.0)	13.8 (26.6)
<i>EORTC QLQ-BR23</i>						
Sexual enjoyment*	49.9 (26.9) n=121	53.0 (29.1) n=132	54.4 (28.3) n=136	56.5 (26.5) n=144	52.5 (26.1) n=115	56.6 (28.8) n=136
Future perspective**	45.8 (31.2)	46.4 (32.8)	49.8 (32.3)	50.9 (31.6)	54.4 (30.1)	54.1 (30.9)
Systemic therapy side-effects**	34.8 (23.1)	35.2 (22.7)	19.3 (15.2)	19.6 (15.6)	18.6 (14.9)	18.3 (15.0)
Hair loss**	29.6 (37.5)	31.7 (39.3)	6.2 (20.4)	6.4 (21.8)	3.8 (20.7)	4.9 (17.1)
EQ-5D-3L***	0.74 (0.22)	0.74 (0.22)	0.75 (0.25)	0.75 (0.24)	0.76 (0.24)	0.77 (0.22)

*EORTC QLQ-C30 Functional scores- range 0-100 (higher score = good functioning)

** EORTC QLQ-C30 Symptom scores – range 0-100 (higher score = worse symptoms)

*** EQ-5D-3L score-range 0-1.

Table 3. Mixed effects models (fixed effects) for the primary QOL outcomes

Outcome	Model variable	Estimate of effects	95% CI	p
Global QOL (C30)	Baseline score	-0.57	-0.63, -0.52	<0.0001
	Age- ref* >70	-	-	-
	- <45	1.12	-3.45, 5.78	0.64
	- 45-54	3.25	-0.62, 7.12	0.10
	- 55-69	3.54	-0.28, 7.36	0.069
	Visit-ref year1	0.75	-0.46, 1.97	0.23
	RT –ref no RT	1.39	-0.92, 3.71	0.24
		Adjusted mean of 'change scores'***	95% CI	p-value***
	RT	8.63	6.86, 10.40	<0.0001
	No RT	7.23	5.46, 9.01	<0.0001
Fatigue (C30)	Baseline score	-0.59	-0.65, -0.54	<0.0001
	Age- ref >70	-	-	-
	- <45	-2.41	-8.07, 3.26	0.40
	- 45-54	-4.14	-8.84, 0.56	0.079
	- 55-69	-3.13	-7.73, 1.47	0.18
	Visit-ref year1	-1.83	-3.20, -0.46	0.0094
	Immediate reconstruction	5.32	0.94, 9.69	0.017
	Ref no recon			0.17
	RT –ref no RT	-1.93	-4.70, 0.84	
	RT	-9.54	-12.19, -6.89	<0.0001
	No RT	-7.61	-10.35, -4.87	<0.0001
Physical function (C30)	Baseline score	-0.41	-0.46, -0.35	<0.0001
	Age- ref >70	-	-	-
	- <45	7.91	3.94, 11.87	<0.0001
	- 45-54	7.06	3.80, 10.32	<0.0001
	- 55-69	4.29	1.06, 7.51	0.0092
	Visit-ref year1	0.20	-0.68, 1.08	0.65
	RT –ref no RT	-0.17	-2.13, 1.79	0.87
	RT	-0.02	-1.53, 1.48	0.97
	No RT	0.14	-1.36, 1.65	0.85
Chest wall symptoms (BR23)	Baseline score	-0.57	-0.62, -0.52	<0.0001
	Age- ref >70	-	-	-
	- <45	4.49	0.59, 8.39	0.022
	- 45-54	1.88	-1.46, 5.22	0.26
	- 55-69	2.36	-0.79, 5.51	0.14
	Visit-ref year1	-1.34	-2.36, -0.31	0.010
	Chemo-ref no chemo	3.74	0.87, 6.61	0.011
	RT –ref no RT	2.17	0.40, 3.94	0.016
	RT	-3.13	-4.74, -1.51	0.0002
	No RT	-5.30	-6.88, -3.71	<0.0001

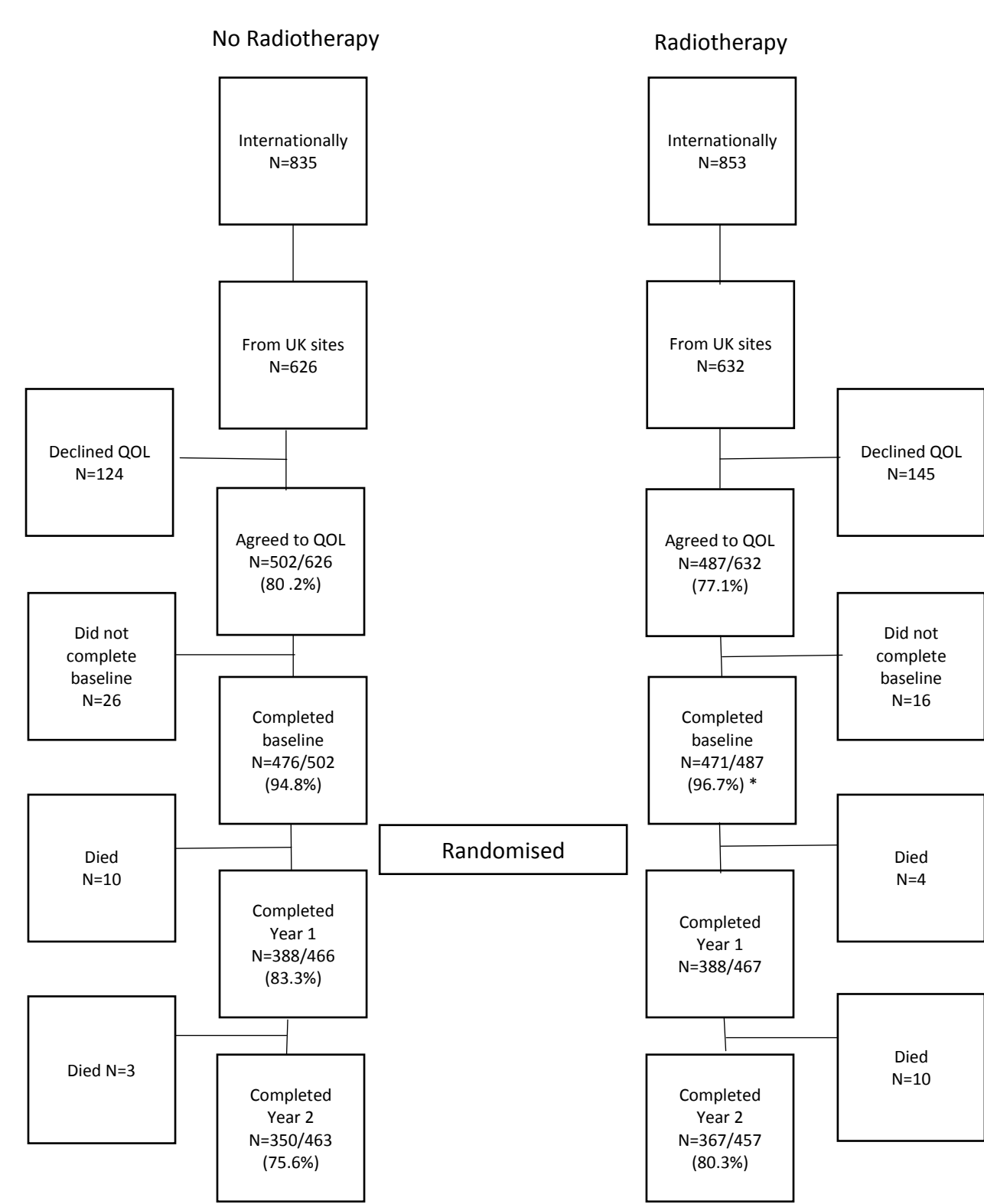
Arm and shoulder symptoms (BR23)	Baseline score	-0.51	-0.57, 0.45	<0.0001
	Age- ref >70	-	-	-
	- <45	0.86	-4.42, 6.14	0.74
	- 45-54	2.89	-1.64, 7.41	0.21
	- 55-69	2.76	-1.51, 7.03	0.20
	Visit-ref year1	-0.93	-2.22, 0.37	0.16
	Chemo-ref no chemo	6.15	2.26, 10.05	0.0021
	RT –ref no RT	-0.53	-2.92, 1.86	0.66
	<i>RT</i>	-1.44	-3.63, 0.75	0.19
	<i>No RT</i>	-0.91	-3.06, 1.24	0.40
Body Image Scale	Baseline score	-0.39	-0.43, 0.34	<0.0001
	Age- ref >70	-	-	-
	<45	1.96	0.53, 3.39	0.0074
	45-54	1.39	0.20, 2.58	0.022
	55-69	0.83	-0.33, 1.99	0.15
	Visit-ref year1	-0.91	-1.28, -0.55	<0.0001
	RT –ref no RT	-0.09	-0.79, 0.61	0.79
	<i>RT</i>	-1.36	-1.90, -0.83	<0.0001
	<i>No RT</i>	-1.27	-1.81, -0.73	<0.0001
HADS-Anxiety	Baseline score	-0.30	-0.35, -0.25	<0.0001
	Age- ref >70	-	-	-
	- <45	1.69	0.86, 2.53	<0.0001
	- 45-54	1.36	0.67, 2.06	<0.0001
	- 55-69	1.21	0.53, 1.90	0.00050
	Visit-ref year1	-0.05	-0.29, 0.18	0.66
	RT –ref no RT	-0.16	-0.57, 0.25	0.44
	<i>RT</i>	0.44	0.13, 0.76	0.0061
	<i>No RT</i>	0.60	0.29, 0.92	0.00022
HADS-Depression	Baseline score	-0.35	-0.41, 0.30	<0.0001
	Age- ref >70	-	-	-
	- <45	0.07	-0.73, 0.87	0.87
	- 45-54	-0.05	-0.72, 0.61	0.88
	- 55-69	-0.04	-0.69, 0.62	0.91
	Visit-ref year1	0.02	-0.16, 0.20	0.94
	RT –ref no RT	-0.14	0.54, 0.25	0.48
	<i>RT</i>	-0.19	-0.50, 0.11	0.21
	<i>No RT</i>	0.05	-0.35, 0.25	0.75
Pain (C30)	Baseline score	-0.51	-0.57, -0.46	<0.0001
	Age- ref >70	-	-	-
	- <45	-0.18	-6.16, 5.80	0.95
	- 45-54	2.76	-2.17, 7.69	0.27
	- 55-69	2.18	-2.70, 7.06	0.38
	Visit-ref year1	0.31	-1.29, 1.91	0.70
	RT –ref no RT	-0.65	-3.62, 2.33	0.67
	<i>RT</i>	0.28	-1.99, 2.56	0.81
	<i>No RT</i>	0.93	-1.35, 3.20	0.42

* ref =reference category in the mixed-effects models

** the adjusted mean for the individual arms is the mean of the 'change scores', (defined as change from baseline to year 1 and from baseline to year 2) in each of the treatment groups, adjusted for baseline score, visit, and age;

***p values - whether each of the means of the 'change scores' within each individual arm is significantly different from zero (i.e., improvement or deterioration in scores from baseline)

Figure 1. CONSORT diagram – Trial profile of SUPREMO patients participating in the Quality of Life (QOL) sub-study



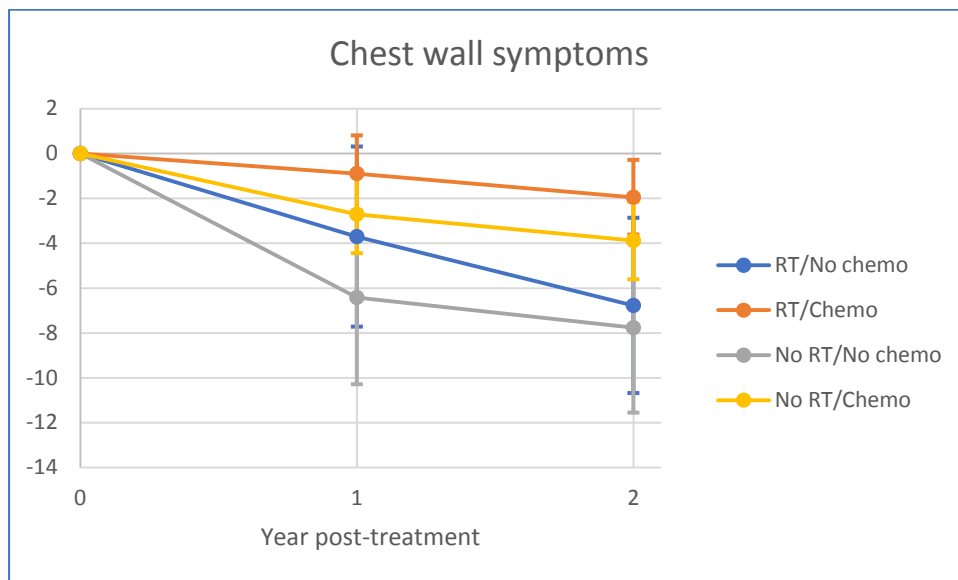
*Note:
1 patient stated RT outside protocol timeframe
4 patients declined RT following randomisation
2 patients began RT but did not complete the

Figure 2. Mean change (95% CI) of QOL scores at years 1 and 2 (adjusted for age group and baseline QOL scores).

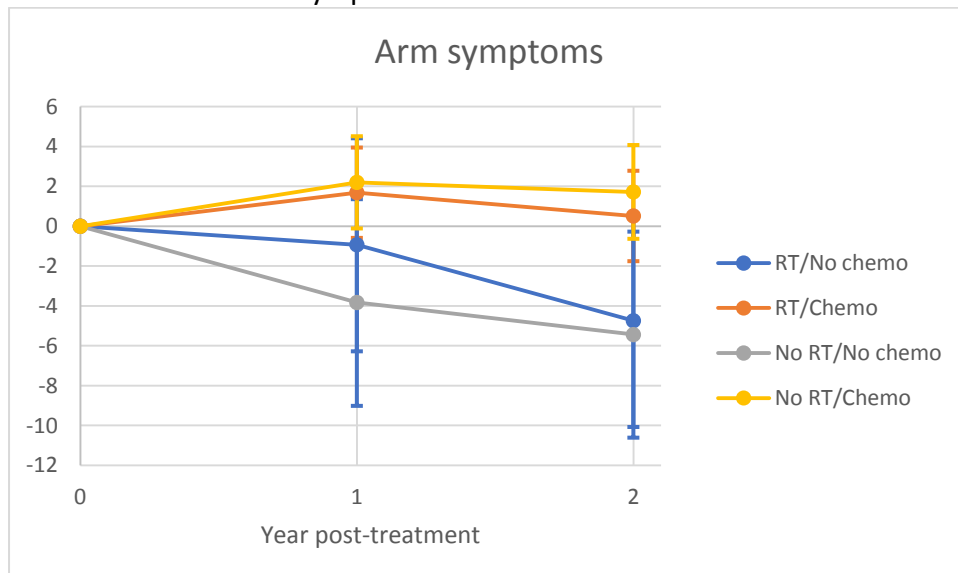
*Symptom scores – range 0-100 with higher score = worse symptoms, negative change score=improvement

**Functional scores and Global QOL - range 0-100 with higher score = good functioning, positive change score=improvement

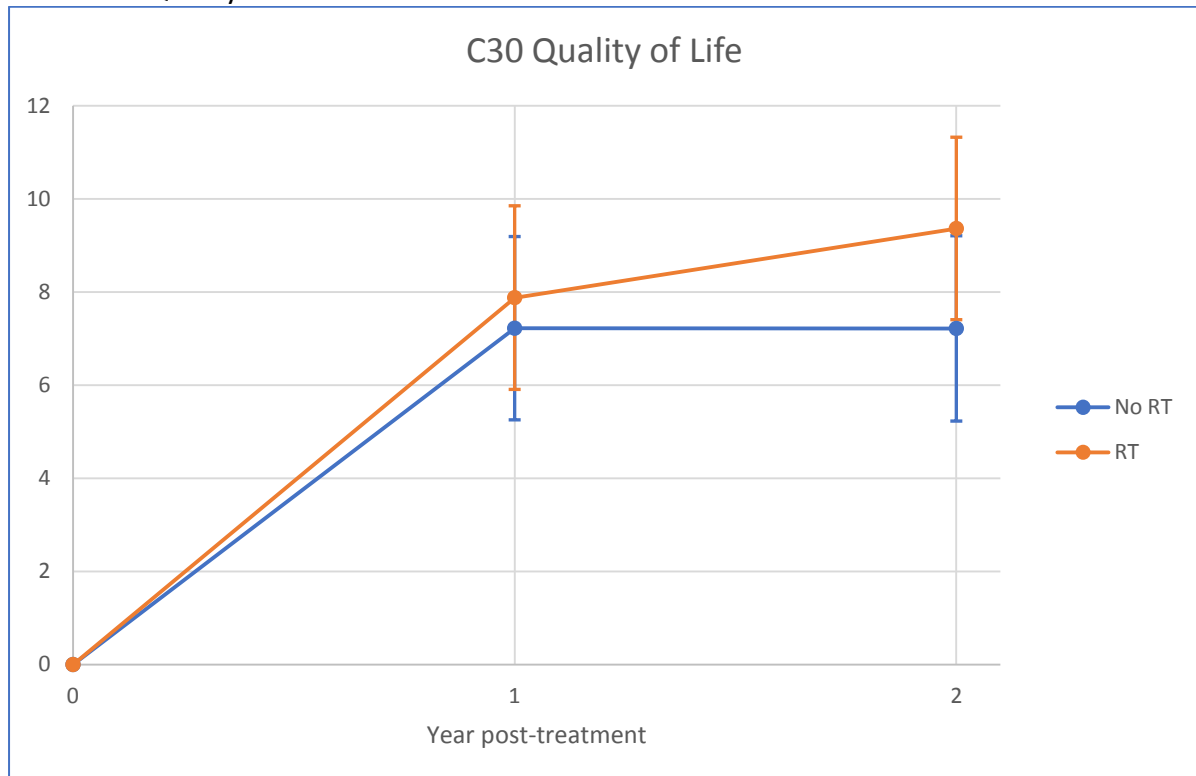
2a. Chest-wall symptoms*



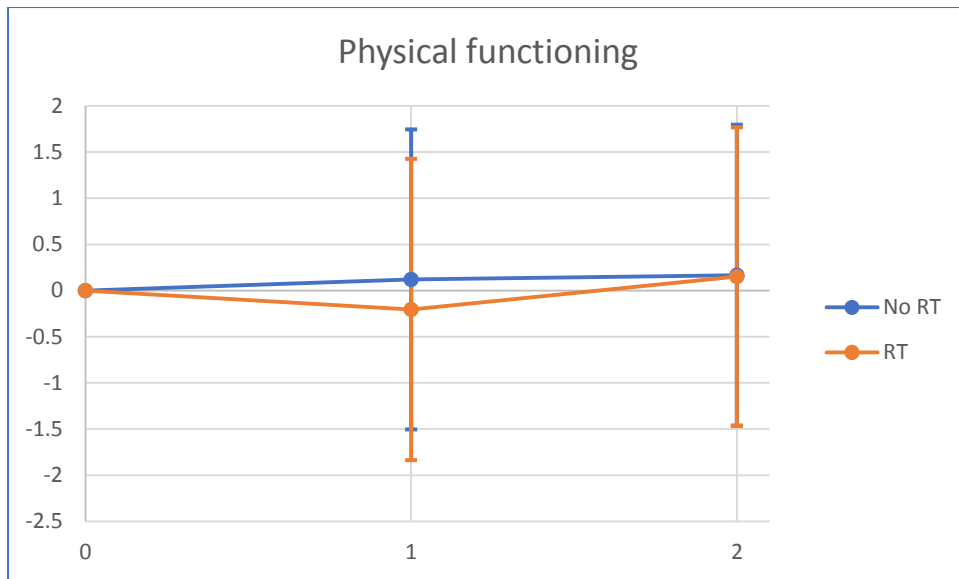
2b. Arm and shoulder symptoms*



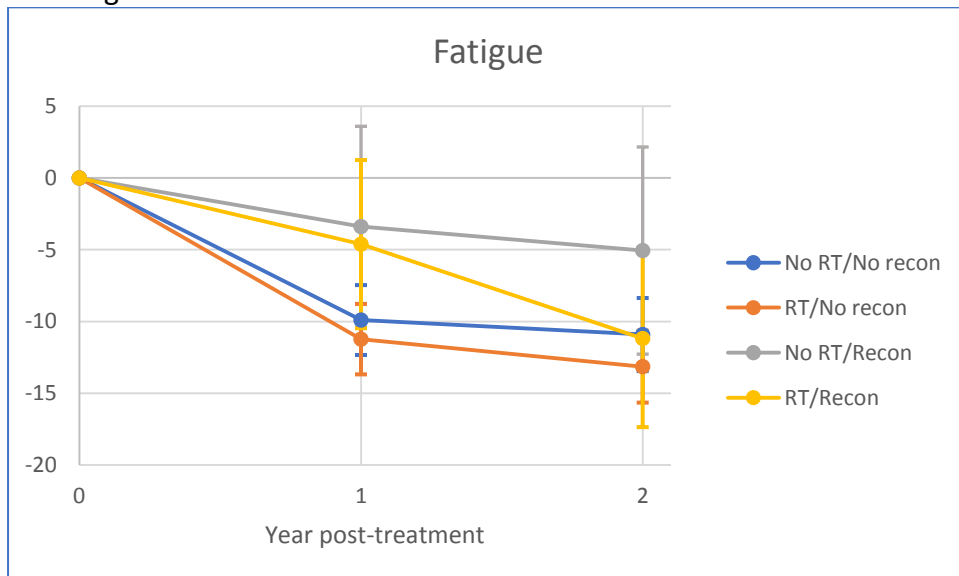
2c. Global Quality of Life**



2d. Physical function**



2e. Fatigue*



Quality of life at 2-year follow-up of SUPREMO randomised trial of post mastectomy radiotherapy for breast cancer

Short title

Quality of life after post mastectomy radiotherapy

Galina Velikova¹, Linda [Jane](#) Williams², Sarah Willis³, J Michael Dixon⁴, Juliette Loncaster⁵, Matthew Hatton⁶, Jacqueline Clarke⁷, Ian H. Kunkler^{8*} and Nicola Russell^{9*} on behalf of the BIG 02-04 MRC EORTC SUPREMO trial investigators

¹ [Prof G](#) Galina Velikova PhD, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds Cancer Centre, St James's University Hospital, Beckett street, Leeds, LS9 7TF, UK

² Linda [Jane](#) Williams PhD, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh UK, Edinburgh, UK

³ Sarah Willis- MSc, London School of Hygiene and Tropical Medicine, Keppel Street, Bloomsbury, Camden, London, WC1E 7HT, UK

⁴ [Prof J](#) Michael Dixon MD, Edinburgh Breast Unit, Western General Hospital, Edinburgh, EH4 2XU, UK.

⁵ Juliette Loncaster FRCR, The Christie Hospital, The Christie NHS Foundation Trust, Wilmslow Rd, Manchester, M20 4BX, UK

⁶ Matthew Hatton, FRCR, Department of Clinical Oncology, Weston Park Hospital, Whitham Rodd, Sheffield, S10 2SJ, UK.

⁷ Jacqueline Clarke, FRCR, Cancer Centre, Belfast City Hospital, Lisburn Road, Belfast, County Antrim, BT9 7AB

⁸ [Prof I](#) Ian H. Kunkler FRCR, Edinburgh Cancer Research Centre, Institute of Genetic and Molecular Medicine, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, UK.

⁹ Nicola S. Russell PhD, Department of Radiotherapy, The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands.

Corresponding author - Galina Velikova PhD, Leeds Institute of Cancer and Pathology, University of Leeds, Leeds Cancer Centre, St James's University Hospital, Beckett Street, Leeds, LS9 7TF, UK

g.velikova@leeds.ac.uk

Tel: +44 113 2067917

*Joint senior authors

Summary

Background Post-mastectomy radiotherapy (PMRT) in patients with 4+ axillary nodes reduces breast cancer mortality, but its role in patients with 1-3 involved nodes is controversial.

Methods BIG2-04-MRC-EORTC SUPREMO is an international parallel randomised controlled trial. Eligible women (over 18 years, with 'intermediate risk' breast cancer, pT1-2N1, pT3N0 and pT2N0 if grade III and/or lympho-vascular invasion, post-mastectomy and axillary surgery) were randomly assigned to receive chest-wall radiotherapy (50 Gy 25 fractions or radiobiologically equivalent 45 Gy 20 fractions or 40 Gy 15 fractions) or not (1:1 ratio). Randomisation was in permuted blocks with varying block length, stratified by centre, without masking of patients or investigators. The primary endpoint is 10-year overall survival. Here, we present the 2-year quality of life (QOL) results (pre-specified secondary endpoint). The QOL substudy, open to all UK patients, consists of questionnaires (EORTC QLQ-C30 and BR23, Body Image Scale, Hospital Anxiety and Depression Scale (HADS) and EQ-5D-3L) completed pre-randomisation, 1, 2, 5 and 10 years. Data were analysed on an intention-to-treat basis, using repeated mixed-effects methods. The trial is registered with International Standard Randomised Controlled Trials (ISRCTN61145589).

Findings

Between August 4, 2006-April 29, 2013, 1688 patients enrolled internationally, 989/1258 (79%) of the UK patients consented to QOL substudy. Patients receiving PMRT reported worse chest-wall symptoms ($p=0.016$) but the difference was small. Symptoms improved from year 1 to 2. Chemotherapy was associated with less improvement. No group differences were observed for arm symptoms, body image, fatigue, pain, overall QOL, physical functioning or HADS scores.

Interpretation PMRT led to more local symptoms up to 2 years post-randomisation, but the difference was small. This data will inform shared decision-making whilst survival results (main trial endpoint) become available.

Funding Medical Research Council, European Organisation for Research and Treatment of Cancer, Cancer Australia, Dutch Cancer Society, Trustees of Hong Kong Shanghai Banking Corporation.

300 words

Research in Context

Evidence before this study

Adjuvant chest-wall irradiation after mastectomy remains a core effective element in the loco-regional management of early breast cancer reducing loco-regional recurrence and breast cancer mortality. While the evidence base for post-mastectomy radiotherapy (PMRT) in patients with 4 or more involved axillary nodes is robust, its role in 'intermediate' risk patients with 1-3 involved nodes is controversial and practices vary. The Oxford overview in 2014 shows an advantage [in overall survival](#) from PMRT in patients with 1-3 positive nodes. However, the generalisability [to contemporary practice](#) of historical trials with different standards of surgery, radiotherapy and systemic therapy remains uncertain. Benefits in survival needs to be balanced against risk of loco-regional and cardio-pulmonary toxicity, particularly in conjunction with potentially cardiotoxic anthracyclines and trastuzumab. The recent American Society of Clinical Oncology guidelines on the use of PMRT emphasizes the importance of evaluating the risk-benefit ratio, but the [overview](#) data is derived from patients treated several decades previously and only a limited number of small studies looked at patient-reported outcomes, such as symptoms and quality of life.

Added value of this study

Our study uniquely investigated the impact of adjuvant PMRT on quality of life in a randomised trial including a large, well characterised population of UK patients with 'intermediate-risk' breast cancer [post-mastectomy](#). At 2 years PMRT was associated with worse self-reported local symptoms (pain, swelling, skin problems in the "area of the affected breast") in comparison with no radiotherapy, but [the difference is small, unlikely to be of clinical significance and](#) the symptoms improved over time. There were no differences in arm symptoms, body image, fatigue, pain, overall QOL, physical functioning anxiety or depression.

Implications of all the available evidence

The impact on PMRT on ~~10-year~~[10-year](#) survival, the primary endpoint of the main SUPREMO trial, will not be known before 2023. In the meantime, both options of administering or omitting PMRT are legitimate for patients in the intermediate risk category (1-3 positive lymph nodes). Our data will inform shared decision-making (as recommended in the recent North American guidelines [on PMRT](#)) and put patients in a better position to make an informed value judgment on what they consider relevant for their situation given the data on the patient-reported symptoms and QOL domains presented in this report. Both physicians and patients may be helped when weighing up the individual estimates of possible benefits of radiotherapy against the impact of PMRT on toxicity and quality of life.

Introduction

Current multimodality treatment for breast cancer has improved survival rates.¹ Avoiding overtreatment and balancing the treatment burden against benefit has become an important research field. Examples of trials investigating selective omission of radiotherapy or chemotherapy have recently been reported.^{2,3} While the impact of mastectomy and chemotherapy on quality of life has been well documented the additional effect of adjuvant radiotherapy following mastectomy is unclear. Chest wall pain, fatigue, anxiety about recurrence and depressive symptoms can all hold back recovery and return to normal activities of daily living.⁴

Adjuvant chest wall irradiation after mastectomy remains a core and highly effective element in the loco-regional management of early breast cancer reducing loco-regional recurrence and breast cancer mortality. While the evidence base for post-mastectomy radiotherapy (PMRT) in patients with 4 or more involved axillary nodes is robust, its role in 'intermediate' risk patients with 1-3 involved nodes is controversial and practice and guidelines vary.⁵ The Oxford overview in 2014 shows an advantage in overall survival from PMRT which included at least the chest wall in the target volume in patients with both 1-3 and 4 or more positive nodes.⁶ However, the generalisability of historical trials with different standards of surgery, radiotherapy and systemic therapy remains uncertain, especially as contemporary survival rates are much higher than in the studies included in the overview. Potential benefits in survival needs to be balanced against risk of loco-regional and cardio-pulmonary toxicity, particularly in conjunction with potentially cardiotoxic anthracyclines and trastuzumab. A recent update by the American Society of Clinical Oncology on the use of post-mastectomy radiotherapy emphasises the importance of evaluating the risk-benefit ratio, particularly in patients with a low risk of local failure.⁷ The benefit of PMRT relies on estimates of recurrence risk, modulated by biological tumour characteristics, weighed against the negative impact of PMRT on the risks of late toxicity (e.g. cardiac toxicity from radiotherapy may be increased by the combination with systemic therapy) ~~Estimates of recurrence risk, and therefore benefit may be modulated by biological tumour characteristics, whereas a negative impact on outcome of excess late toxicity may be significant (e.g. cardiac toxicity from radiotherapy may be increased by the combination with systemic therapy).~~⁸ The data currently available on these modulating effects is derived from patients treated several decades previously.

Selective use of post-mastectomy radiotherapy is being evaluated in the BIG 2.04 MRC ~~FEORTC~~ SUPREMO trial ~~(ISRCTN61145589)~~, which assesses the effects of adjuvant chest wall radiotherapy without axillary irradiation in patients with 'intermediate risk' early breast cancer who have undergone mastectomy and adequate systemic therapy following contemporary guidelines for all treatment modalities. This is the largest randomised trial to date to assess the role of PMRT in this subset of patients. The endpoints have been previously described.⁹ In brief, the primary endpoint of the trial is overall survival at 10 years. Secondary end points include various breast cancer recurrence endpoints, toxicity, acute and late morbidity (cardiac morbidity and mortality) and quality of life. Sub-studies include the TRANS-SUPREMO seeking molecular markers of radiosensitivity, a cardiac ~~sub-study~~ substudy, and for UK patients only Quality of Life (QOL) assessment and Health Economics evaluation. These sub-studies will provide an important high-quality evidence base on the balance of potential benefits and treatment burden, to support patients and health care professionals during shared decision-making.

The long-term impact of breast cancer and its treatment on everyday life has been identified as a critical knowledge gap and a key priority for breast cancer research¹⁰. For radiotherapy, there is a limited information on treatment impact. A small number of trials have investigated self-reported breast, arm, and shoulder symptoms, functional outcomes and quality of life after radiotherapy, predominantly in breast conserving therapy¹¹⁻¹³. Patients usually report transient and short-term effects of radiotherapy, with relatively limited effect on overall quality of life^{14,15}.

No comprehensive QOL data exists in patients having ~~post-mastectomy radiotherapy~~ (PMRT and only a few studies have compared patient-reported outcomes following breast-conserving surgery versus mastectomy with and without reconstruction. Recent introduction of oncoplastic surgical techniques is expected to have an impact on post-treatment morbidity and patient satisfaction with body image^{16,17}. There is a dearth of level 1 evidence assessing the impact of adjuvant post-mastectomy radiotherapy on quality of life QOL of patients who have undergone reconstruction.

The SUPREMO QOL ~~sub-study~~ substudy aimed to examine the effects of PMRT on several primary QOL outcomes (global QOL, fatigue, physical function, chest wall, shoulder and arm symptoms, body image, anxiety and depression) at 1, 2, 5, and 10 years post treatment. Here we report the 2-year results. To our knowledge, this is the first study looking at the impact of adjuvant radiotherapy on QOL in a large randomised trial confined to patients treated by mastectomy for early breast cancer (including patients undergoing breast reconstruction).

Methods

~~Patients and Procedures~~ Study design and Participants

SUPREMO was an open label parallel randomized trial. Patients provided written informed consent before enrolment. The full eligibility, exclusion criteria and trial procedures are described in the trial protocol provided in the supplementary web material and online (<http://www.supremo-trial.com/SUPREMO%20protocol%20version29.pdf>). ~~Briefly, patients were~~ Briefly, eligible patients were women aged 18 years or older if they had undergone mastectomy for unilateral breast cancer, and an axillary staging procedure with axillary lymph node dissection, if node positive. Patients with 'intermediate risk' breast cancer were eligible, defined as pT1-2N1, pT3N0 and pT2N0, if also grade III and/or with lympho-vascular invasion on histology. Patients needed to be fit for surgery, radiotherapy or adjuvant systemic therapy. Exclusion criteria included previous or concurrent malignancy (except non-melanomatous skin cancer and carcinoma in situ of the cervix), ductal carcinoma in situ, bilateral breast cancer, pregnancy at the time of radiotherapy treatment and male gender.

All patients had to receive adequate systemic therapy following contemporary guidelines depending on patient and tumour characteristics. If this included chemotherapy, treatment regimes containing at least 4 cycles of anthracyclines were recommended. Adjuvant trastuzumab was given according to local practice. In 2011 the eligibility criteria were widened, following a protocol amendment (version 29 August 30, 2010) approved by the Ethics Committee, to include neo-adjuvant chemotherapy.

Eligible patients were randomly assigned to receive chest-wall radiotherapy or not (1:1 ratio). For patients randomized to chest wall radiotherapy, radiation was given after the chemotherapy (when given). Radiotherapy treatment consisted of chest wall radiation to a total dose of 50 Gy in 25 daily fractions of 2 Gy over 5 weeks. Other permitted radiobiologically equivalent schedules ~~included were~~ 45 Gy in 20 fractions over 4 weeks, and 40 Gy in 15 fractions over 3 weeks. Guidelines on treatment planning and set up were given, and there was a radiotherapy quality assurance programme in the trial. The use of bolus was permitted and had to be pre-specified per centre. Axillary irradiation was not permitted, but medial peri-clavicular and/or internal mammary chain irradiation was permitted according to local policy of the centres. Boost radiation was not permitted. Surgery, systemic therapy and pathology were also subject to pre-specified quality assurance. Additional recorded data included cardiovascular risk factors, radiotherapy cardiac and lung exposure parameters, systemic therapy (type, doses, dates) and any reconstructive surgery (type, immediate or delayed). Patients with gross protocol violations (e.g. margins involved or less than 1mm for invasive cancer or DCIS) will be removed before the final analysis of the main trial. A mammogram of the opposite breast, if appropriate, was recommended at least in alternate years for 10 years from the date of

mastectomy. The primary endpoint of the trial, overall survival, is not centrally reviewed. Serious adverse events were to be reported if they occurred during radiotherapy or within 30 days of the last radiotherapy session (fraction) whether or not they were related to the randomised treatment. Any toxicity assessed as a grade 4 or 5 acute or late morbidity score had to be reported on a SAE/SUSAR form for the entire follow up period of the trial. Adverse events were reviewed by the Data Monitoring and Ethical Committee meeting every 6 months (or as often as they considered appropriate). Monitoring (source data verification) is carried out by the Cancer Clinical Trials Team in Edinburgh on 10% of the patient data of the main trial with site visits allowed in the UK. Higher levels of monitoring will be performed, if requested by the Data Monitoring Committee, or if particular safety issues are identified by the investigators, the trial management group of the trial steering committee.

The study was approved by the Multi-Centre Research Ethics Committee, Edinburgh (MREC 05/50501/106) and local research and development offices. Patients provided written informed consent before enrolment and had additional options to consent to the sub-studies, including QOL substudy.

Randomisation and masking

~~SUPREMO was an open-label trial.~~ Consenting patients were randomized post-operatively to either chest-wall radiotherapy or no chest-wall radiotherapy (1:1 ratio). Patients were randomised by permuted blocks with the block length being varied randomly to minimise the effect of entry bias. Stratification was by treatment centre due to possible between centre differences in the manner in which radiotherapy is given. There was no masking by patients or investigators. Randomisation was performed via a telephone call to The Information and Statistical Division (ISD) at National Services Scotland.

Procedures for QOL sub-study

~~QOL sub-study~~

All patients eligible for SUPREMO from UK centres were invited to participate in the QOL study. Patients who provided informed consent ~~ed~~ completed a questionnaire booklet in the clinic before randomisation. Completed booklets were sent to the trial's office and subsequent questionnaires were posted to patients at 12 and 24 months by the trial's office. If the baseline questionnaire was not returned to the trial's office further questionnaires could not be sent, as patients' names and addresses were not available to the trial co-ordinator. Reminders were sent to the hospitals where baseline questionnaires were overdue. No reminders were sent to patients at 12 and 24 months.

QOL was assessed using several well-validated questionnaires.

EORTC QLQ-C30 (version 3.0) and the breast module QLQ-BR23 (version 1.0). The QLQ-C30 consists of 30 questions addressing 5 functional scales (cognitive, emotional, physical, social, and role), 9 symptom scales (appetite loss, constipation, diarrhoea, dyspnoea, fatigue, financial difficulties, insomnia, nausea and vomiting, and pain), and one Global Health Status/QOL scale¹⁸. The EORTC QLQ-BR23 focuses on breast cancer specific issues and includes 23 questions addressing 4 functional: body image, future perspective, sexual enjoyment, and sexual functioning and 4 symptom scales: arm symptoms (swelling in arm or hand, arm or shoulder pain, and difficulty ~~raising~~moving the arm), breast/chest wall symptoms (pain, swelling, oversensitivity, and skin problems in the area of the affected breast), systemic therapy side-effects, and upset by hair loss¹⁹. All scores for the EORTC QLQ-C30 and EORTC QLQ-BR23 were transformed to a scale from 0 to 100. Higher scores on the functional scales and Global QOL represent a superior level of functioning and better QOL, whereas higher scores in the symptom scales or items represent worse symptoms.

The Body Image Scale (BIS) is a 10-item scale designed specifically for use with cancer patients to assess aspects of attractiveness, sexual attractiveness and feelings or satisfaction with appearance. Scores were graded 0-3 and summed to produce a single score, where a higher score indicated more problems (score range from 0 to 30)²⁰.

Hospital Anxiety and Depression Scale (HADS) is a 14-item instrument with two sub-scales for anxiety and depression²¹. Scores range from 0 to 21 on each scale, with higher scores indicating more distress. Scores above 11 suggest probable cases of anxiety or depressive illness, and scores between 8 and 10 indicate borderline cases. A combined score of 19 or above is considered indicative of psychological distress.

EQ-5D-3L questionnaire measures health status across five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Respondents specify whether they have no problems, some problems or severe problems within each domain, on the day of response. These EQ-5D-3L health states descriptions are converted into a single summary index (range from 0 to 1) by attaching a value to each of the levels in each dimension. As is standard practice, these values were obtained from a large UK population study using a choice-based method of valuation.²² The resulting summary score, or utility value, can then be used directly in the cost-utility analysis.

Outcomes

The primary endpoint of SUPREMO trial is 10-year overall survival. Quality of life is a secondary endpoint alongside chest-wall recurrence, regional recurrence, disease free survival, acute and late morbidity and cost-effectiveness. In the QOL substudy we pre-specified as primary outcomes global QOL, fatigue, physical function, chest wall symptoms, shoulder and arm symptoms, body image, anxiety and depression. Secondary outcomes are role, social, sexual functioning, pain and nausea/vomiting.

Sample Size

~~Sample size for the SUPREMO QOL study was considered as a problem of estimation rather than a significance testing. With 200 evaluable patients per group the proportion of patients exhibiting a particular side-effect or specified degree of morbidity in a QOL domain could be estimated with a standard error of 3.5% or less. The corresponding difference between the groups could be estimated with a standard error of 5% or less. However, as there is usually a significant attrition over time, in order to have sufficient numbers by 10 years a target of 800 patients was set. The total sample size of SUPREMO was reduced during the course of the trial, following a protocol amendment approved by the ethics committee, from 3500 to 1600 but this did not affect the QOL sub-study sample.~~

Statistical analysis

Sample Size

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sample.

When calculating QOL questionnaire or sub-scale scores, we followed official questionnaire guidelines on handling missing individual items. In general, if more than 50% of the items were

missing, sub-scale scores were not calculated (missing); if less than 50% of items were missing, those were replaced by the mean of the answered items and a score was calculated. Where no guidance existed, that score was recorded as missing.

In order to maintain the Normality of the residuals, the difference from baseline to each subsequent questionnaire was calculated for each scale. Repeated analysis of covariance was conducted using PROC MIXED, to allow for observations that are missing at random. Time and treatment allocation interactions were tested for each scale but are to be reported only where statistically significant. Baseline scores were included in each model as a covariate. As the QOL study was not originally powered for hypothesis testing, p-values are only included for illustration. However, the treatment with radiotherapy was our primary outcome, and any results that have a p-value of ≤ 0.05 with this variable will be discussed. Due to the large number of models, clinical variables will only be discussed if they exceed the more conservative threshold value of 0.01.

The principal analysis modelled the change in score in the pre-specified QOL outcomes (global QOL, fatigue, physical function, chest wall, shoulder and arm symptoms, body image, anxiety and depression) by time (visit 1 at 12 months or 2 at 24 months) of follow up, age group (<45, 45-54, 55-69, ≥ 70), baseline score and treatment (\pm radiotherapy).

As almost all patients received some form of systemic therapy and some underwent breast reconstructive surgery, secondary exploratory analyses were performed to evaluate whether these treatments influenced the QOL outcome measures. The secondary analysis included clinical covariates also considered to have an impact on QOL (extent of axillary surgery, early breast reconstruction, adjuvant chemotherapy, adjuvant hormonal therapy and trastuzumab). This was performed by creating a basic model of age group, time and baseline score, then adding the clinical variables in turn to create a model of best fit. This process was then repeated until no variables added significantly to the model. The radiotherapy variable was then added to the best fit model. Only patients with complete data for all clinical variables were included in this modelling.

All analyses were on an intention to treat basis. No additional sensitivity analyses or interim analyses were planned for this stage of the trial. The analysis was generated using version 9.4 of the SAS System for Windows (www.sas.com Copyright © 2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.)

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN61145589.

Role of Funding Source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and the joint senior authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between August 4, 2006 and April 29, 2013 the trial recruited 1688 patients internationally. All patients eligible for SUPREMO from 111 UK centres were invited to participate in the QOL substudy (n=1258). This approach was adopted in order to avoid any bias in selecting centres or patients. The consent rate between centres varied (see Table consent rates in the web appendix, page 1). The majority of the centres (73 centres) had consent rates of 80% or above. Ten centres did not include any of their 66 patients in the QOL study. –of which 1258 were from UK centres and eligible for the QOL study. A total of 989 (79%) UK patients consented to participate, of them 95.7% (947/989) patients (returned the baseline questionnaires (476/502 94.8% in the control and 471/487 96.7% in

the radiotherapy arm). The statistical analysis is based on 947 patients who returned the baseline QOL questionnaires (Figure 1). Due to the practical arrangements for the QOL data collection, questionnaires for years 1 and 2 could be sent only to patients who returned the baseline questionnaire. We have not formally recorded reasons for declining participation as according to the Ethics Committee approved patient information sheet, patients were not obliged to provide such reasons. The patients from UK who declined participation or did not return the baseline questionnaires were older (n=311 mean age 57.7 years, SD 11.9) than those who consented and returned the baseline questionnaire (n=947 mean age 56.1 years, SD=11.0; p=0.02). Comparing the age of QOL study participants with the rest of the main trial (UK patients not participating in QOL study and all patients from other countries) did not show an age difference (n=741 mean age 55.6 years, SD 11.6, p=0.34). In order to check further for potential bias in patient selection for the QOL substudy, we compared the clinical characteristics of the patients completing the QOL substudy with those of the patients in the main trial in Table 1.

Good patient compliance was achieved with the completion of QOL measures: ~~at 947 patients (95.7%) returned the baseline questionnaires (476/502 94.8% control and 471/487 96.7% in radiotherapy)~~ year 1 388/466 83.3% in the control group and 388/467 83.1% in the radiotherapy group; ~~at~~ year 2 (350/463 75.6% and 367/457 80.3% respectively). A slightly better compliance was observed in the radiotherapy arm at baseline and year 2 (Figure 1).

Median follow-up for the patients who returned the baseline questionnaires was 748 days (interquartile range 417-763) for the control group and 749 days (interquartile range 725-762) for radiotherapy group.

Patient characteristics

Patients demographic, clinico-pathological characteristics and treatment details are shown in Table

1. There is good balance in clinical characteristics between the radiotherapy and no radiotherapy groups in the QOL substudy. Some 70% (669/947) of patients had T2 tumours, 54% (512/947) were Grade 3, 78% (746/947) were ductal carcinomas, 19% (180/947) were oestrogen/progesterone receptor negative, and 30% (285/947) Her2 positive. Only a small proportion of 11% (11/947) had immediate reconstruction, and 11% (106/947) late reconstruction (by 2 years). A further review of the type of breast reconstruction suggested more frequent autologous reconstructions in the radiotherapy group, whereas there were more reconstructions with an implant/expander in the control group (see Web appendix, page 2). This trend was observed for both the immediate and the late reconstructions. Some 84% (796/947) of participants had adjuvant chemotherapy, 19% (183/947) trastuzumab and 75% (712/947) endocrine therapy. Two-thirds of patients had T2 tumours, slightly over half were Grade 3, over 78% were ductal carcinomas, approximately 20% were oestrogen/progesterone receptor negative, and 30% Her2 positive. Only a small proportion of just over 10% had immediate reconstruction, and 10% late reconstruction (by 2 years). A further review of the type of breast reconstruction suggested more frequent autologous reconstructions in the radiotherapy group, whereas there were more reconstructions with an implant/expander in the control group (see Web appendix, page 2). This trend was observed for both the immediate and the late reconstructions. Over 80% of participants had adjuvant chemotherapy, 20% trastuzumab and over 70% endocrine therapy. No differences are observed between the QOL participants and the full trial.

The majority of patients in the radiotherapy group of the QOL study received 40 Gy in 15 fractions (69%, 327/478), with the remaining patients equally divided between 50 Gy in 25 fractions (11%, 52/478), 45 Gy in 20 fractions (10%, 48/478) and other/unknown (10%, 51/478). In the main trial, a smaller proportion of 52% (445/853) received 40 Gy in 15 fractions, a larger proportion of 27% (227/853) had 50 Gy in 25 fractions, 7% (57/853) had 45 Gy in 20 fractions and 15% (124/853) - other/unknown. The dose for all EORTC centres was 50 Gy in 25 fractions.

Baseline and follow-up QOL scores are shown in Table 2. Baseline scores were reported following surgery and prior to randomisation. Of note, patients reported relative impairment in global QOL with a mean score of 60 (100 is excellent), a high level of fatigue (mean of 40, where 100 is greatest degree of fatigue), insomnia (mean of 36-37; 100 is worse) and a degree of arm symptoms, chest wall symptoms and pain (in the range of 17 to 24; 100 is worst symptom).

Pre-specified primary QOL outcomes

Table 3 presents the results from mixed-effects models analysis of pre-specified primary QOL outcomes and pain (a pre-specified secondary QOL outcome). The tested clinical variables are included in Table 3 where they were found to have a significant effect ($p < 0.01$) on either the radiotherapy treatment or on changes over time. Such effects were found for adjuvant chemotherapy and immediate breast reconstruction but not for extent of axillary surgery, adjuvant endocrine therapy or trastuzumab.

Chest wall symptoms were significantly worse in the group receiving radiotherapy (estimate of effect 2.17; 95% Confidence Interval (CI) 0.40, 3.94; $p = 0.016$). There was an improvement between years 1 and 2 (visit effect -1.34; 95% CI -2.36, -0.31; $p = 0.010$), but the improvement was smaller in the radiotherapy group (Figure 2a). Of Age had a significant effect: symptoms in older patients showed greater improvement than in patients aged under 45 years. From the clinical factors the use of chemotherapy was associated with less improvement in chest wall symptoms but there was no interaction with radiotherapy, suggesting an additive effect of chemotherapy (Figure 2a). There was a borderline age effect, with patients <45 years having worse chest-wall symptoms than those ≥ 70 years (estimate of effect 4.49; 95% CI 0.59, 8.39; $p = 0.022$).

Arm problems did not differ significantly according to radiotherapy treatment (Figure 2b), they improved over time in both group between years 1 and 2, with a greater improvement in older patients (data not shown). When clinical variables were included the effect of age was no longer significant apparent. However, chemotherapy had an significant effect with patients receiving chemotherapy showing less improvement of arm symptoms over time, suggesting that chemotherapy and age were confounders. Significantly more patients who received chemotherapy were in the younger age group (97% of patients <45 years, 97% in 45-54 years, 85% in 55-69 years, 37% in ≥ 70 years groups, $P < 0.0001$). Contrary to the clinical expectations, the extent of axillary surgery (comparison of 3 types: 1) sentinel node biopsy or node sampling; 2) sentinel node biopsy plus axillary node clearance; 3) axillary node clearance) did not have an effect on arm/shoulder symptoms scores (see Web appendix, page 3). Furthermore, the extent of axillary surgery did not have an impact on any of the pre-specified QOL variables, except a trend for higher HADS-Anxiety in patients with sentinel node biopsy plus axillary node clearance.

Despite the observed differences in chest-wall symptoms patients reported relatively few body image problems with improvement between years 1 and 2 over time. Some age effect was observed with patients <45=54 years old reporting more concerns about their body image in comparison with patients ≥ 70 years old (estimate of effect 1.96; 95% CI 0.53, 3.39; $p = 0.0074$).

The overall quality of life QOL of patients was not affected by radiotherapy treatment. Furthermore, improvement in overall quality of life was observed between baseline and year 1 with further but smaller improvement by year 2 (Figure 2c).

Physical function was not affected by treatment and no change was observed over time (Figure 2d). As expected there was an age effect with the younger age group reporting better overall physical functioning (Table 3).

Patients reported high baseline level of fatigue, likely due to the preceding surgery, but without differences between the treatment groups. Significant improvement between year 1 and 2 was observed over time was observed. Immediate reconstruction had a borderline significant impact on

the ~~change scores at year 1 (estimate of effect 5.32; 95% CI 0.94, 9.69; p=0.017)~~rate of improvement ~~showing a slower improvement particularly at year 1~~, possibly related to slower recovery from the operation (Figure 2e), but without detectable differences in overall ~~quality of life~~QOL or body image.

No group differences were seen in HADS-Anxiety and HADS-Depressions scores. Women younger than 70 reported higher levels of Anxiety with improvement ~~from baseline to over year 1 and to year 2 time in both groups.~~

Pre-specified secondary QOL outcomes

An interesting pattern in self-reporting of general pain was observed. The mean score at baseline was just over 20 in both groups, but without any ~~significant~~ improvement ~~from baseline to year 1 or year 2 over time~~ independent of randomisation arm, which is at odds with ~~some of the findings for the primary outcomes (global QOL, fatigue, chest-wall symptoms, body image and anxiety) where we observed an improvement from baseline~~the other findings. We investigated the ~~potential effects~~ impact of systemic treatments. Borderline effects were found for use of trastuzumab (P=0.06) and chemotherapy (P=0.08), possibly associated with the use of taxanes. No ~~significant~~ effect was found for endocrine therapy (none vs tamoxifen vs aromatase inhibitors).

No between-group differences were observed for nausea/vomiting, sexual, role and social functions. Gradual improvement over time was observed without any effect of treatments. Role function and social function showing the biggest numerical improvement over time, in year 1 with continued improvement in year 2. Patients having radiotherapy ~~had significantly bigger~~reported larger improvements in their social function in comparison with those who did not. ~~(details in online Appendix).~~Patients reported very low scores on sexual functioning (mean of 11 out of 100). ~~We had good completion rate for the general sexual function questions 97% (914/947) but only 27% (253/914) patients completed the conditional sexual enjoyment questions at baseline~~ suggesting that the vast majority of patients are not sexually active. ~~This is supported by the fact that only about 25% responded to the optional question on sexual enjoyment~~(Table 2). These observations are consistent with other reports.

~~The e~~Exploratory analysis of the other scales ~~are-is~~ in ~~the web online~~ appendix page 5. All remaining scales and items did not show any impact of radiotherapy treatment and all show improvement or stability over time.

Discussion

To our knowledge, this is the first study investigating the impact of adjuvant radiotherapy on quality of life after mastectomy in a large randomised trial including a ~~substantial~~large, well characterised population of UK patients with 'intermediate-risk' breast cancer. The key finding is that PMRT was associated with worse local self-reported symptoms (pain, swelling, oversensitivity and skin problems in the "area of the affected breast") in comparison with no radiotherapy, although these symptoms improved over time. ~~The estimated effect is small, with a difference in 'change scores' between the radiotherapy and control group of 2.17 points; 95% CI 0.40, 3.94. There is published data on EORTC QLQ-C30 on 'change scores' within groups or 'scores difference' between groups that is clinically significant, but to the best of our knowledge, there is no such available data on EORTC-BR23 scores~~²³. We opted to present the mean scores and standard deviations in order to allow comparisons with other studies. In an attempt to explore the clinical significance of the observed statistically significant difference, we looked at using a generic approach of 0.5 of the standard deviation to indicate minimally important difference. Therefore, we calculated the standard deviation of the 'change score' for chest wall symptoms from baseline to year 1 in the control group.²⁴ The standard deviation was 17.3 and a score 8.65 is likely to indicate a clinically meaningful difference. The observed difference of 2.17 is relatively small and unlikely to be of clinical significance, which is of course reassuring for patients and clinicians. Recent guidelines from Federal Drugs Administration (FDA) recommend establishing a meaningful change in patient reported

outcomes measures at the individual level (i.e., defining a responder) versus at the treatment group level²⁵. The definition of a responder being “a score change in a measure, experienced by an individual patient over a predetermined time period that has been demonstrated in the target population to have a significant treatment benefit”. Using this approach and a ‘change score’ of 8.65 as a cut-off score for clinical significance we applied ‘responder analysis’ (web appendix page 7). We calculated proportions of patients whose scores ‘improved’ by < -8.65 points between baseline and year 1, those who remained ‘stable’/no change’ (change score= ± 8.65) and those whose scores ‘worsened’ by $> +8.65$ points. This ‘responder analysis’ showed that 16.3% (63/386) of patients receiving radiotherapy reported clinically meaningful worse ‘change score’ vs 11.9% (46/385) of those without radiotherapy. In other words, 4.4% more patients on radiotherapy experience worse chest wall symptoms than those not receiving PMRT. This way of interpretation of results may be more informative to clinicians and patients, but a note of caution is appropriate due to the assumptions described above.

²⁶There was no **impact of radiotherapy to the chest wall** on arm symptoms (axillary radiotherapy was prohibited in the trial), body image, overall QOL, physical function, fatigue or symptoms of anxiety or depression. Exploratory analyses showed that systemic chemotherapy treatment had an additive **borderline** effect on patients’ chest wall and arms symptoms but without an interaction with the radiotherapy treatment. This is consistent with other studies²⁷.

Sentinel node biopsy procedure is the current standard surgical staging procedure for the axilla. In SUPREMO about a quarter of patients (those with pN0 (sn) tumours) in the main and QoL substudy underwent limited axillary surgery (sentinel node biopsy or nodal sampling). The extent of axillary surgery had no impact on any of the pre-specified QOL outcomes, including arm symptoms. This is perhaps an unexpected finding and could be due to lack of sensitivity of the EORTC BR23 scale (which has 3 items on ‘pain in arm or shoulder’, ‘swollen arm or hand’ and ‘difficulty raising your arm’). The impact of radiotherapy to the axilla on arm symptoms cannot be evaluated in the SUPREMO trial, as this was prohibited. Our findings are not generalisable to women who were treated with both an axillary nodal dissection and regional nodal radiotherapy. This treatment is generally reserved for patients with higher nodal load (N2 and N3 disease) than included in the SUPREMO trial (pN0 or pN1).

Neo-adjuvant treatment was allowed in a later protocol version (version 29), but the number of treated patients is too small (n=8) for valid conclusions and therefore we did not perform any between group comparisons.

We observed a low rate of immediate breast reconstruction (only 111 patients). ~~T~~_I this procedure was associated with higher fatigue levels and slower recovery in comparison with no immediate reconstruction but no impact on body image or the other QOL outcomes. **The estimated effect of immediate reconstruction on fatigue was 5.32, corresponding to a small clinically meaningful difference²³**. This was an exploratory analysis and we used a generic QOL and body image questionnaires rather than breast-reconstruction instruments (such as BREAST-Q), which is likely less sensitive to specific outcomes¹⁷.

The observed low levels (11%) of reconstructive surgery (either immediate or delayed to year 2) should be noted. This likely reflects the pattern of care in the period of the SUPREMO trial recruitment (2006-2013) or may be due to concerns of entering patients who had reconstruction into a trial of radiotherapy. There appears to be a trend in using more autologous procedures in patients who had radiotherapy and more implants/expanders in those not receiving radiotherapy. Due to the small number of reconstructions, SUPREMO trial cannot provide useful information on the impact of radiotherapy on breast reconstruction. We are collecting further information on delayed (beyond 2 years) reconstructions, which will be analysed at 5 and 10 years and provide valuable information on rates of breast reconstruction across the UK, as well as its impact on patients’ experiences and satisfaction with body image. Furthermore we do not have the power to

assess between group differences taking into account the dose schedules in the radiotherapy group. A direct comparison of conventional versus hypo-fractionation for chest wall radiotherapy after breast reconstruction is being carried out in North America by the Alliance for Clinical Trials in Oncology (NCT03414970). The primary objective is to evaluate whether the reconstruction complication rate at 24 months post radiation is non-inferior with hypofractionation. The trial is ongoing and will complete recruitment in 2021, with final results in August 2025.

Due to the low rates of reconstruction in SUPREMO, we do not have the power to assess between group differences taking into account the dose schedules in the radiotherapy group. A direct comparison of conventional versus hypo-fractionation for chest wall radiotherapy after breast reconstruction is being carried out in North America by the Alliance for Clinical Trials in Oncology (NCT03414970). The primary objective is to evaluate whether the reconstruction complication rate at 24 months post radiation is non-inferior with hypofractionation. The trial is ongoing and will complete recruitment in 2021, with final results in August 2025.

It should be noted that the observed levels of reconstructive surgery (either immediate or delayed to year 2) are low in the range of 10-13%. This likely reflects the pattern of care in the period of the SUPREMO trial recruitment (2006-2013) or may be due to concerns of entering patients who had reconstruction into a trial of radiotherapy. There appears to be a trend in using more autologous procedures in patients who had radiotherapy and more implants/expanders in those not receiving radiotherapy. Due to the small number of reconstructions, SUPREMO trial cannot provide useful information on the impact of radiotherapy on breast reconstruction, and further evidence is needed. We are collecting further information on delayed (beyond 2 years) reconstructions, which will be analysed at 5 and 10 years and provide valuable information on rates of breast reconstruction across the UK, as well as its impact on patients' experiences and satisfaction with body image.

Most of the published literature relating to the impact of adjuvant radiotherapy on **quality of life QOL** relates to non-randomised **studies**, often of small size, which may be subject to selection bias **and neither and neither** surgery, radiotherapy or systemic **treatments** were subject to pre-specified quality assurance. Comparisons are often difficult because of differing types of surgery, stage of disease, QOL measures **s** used and time-points of QOL assessment. **The Ss** studies often included both patients treated by mastectomy and breast conserving surgery. The START trial looked at late effects of different schedules of radiotherapy at 5 years and found that up to a third of women reported moderate or marked pain in the arm and shoulder and more than 10% experienced arm/hand swelling¹². The trial included a small number of mastectomy patients (about 20%) and although the QOL results are consistent with ours, they are not directly comparable **since only 10% had chemotherapy and 20% had regional nodal irradiation in addition to breast/chest wall radiotherapy**. The experience of breast/arm symptoms over 5 years represents chronic morbidity that has stronger association than cosmesis with long-term quality of life, making these important outcomes in clinical trials²⁸.

A more recent multicentre study from Korea in 1156 patients (541 breast conserving surgery and 43 mastectomy) using the EORTC measures showed poorer QOL with pain, discomfort and anxiety during radiotherapy, with improvement over a 3 year period. However, the number of mastectomy patients was very small. The Moving Beyond Cancer psychosocial intervention trial studied the QOL of 558 women with stage 1 and 2 breast cancer treated with surgery **alone** (breast conserving **or /mastectomy) alone**, surgery with radiation, or surgery followed by chemotherapy and radiation over 1 year, using SF-36 **questionnaire**. Similar to our study, physical and psychosocial function improved significantly over time. However, the measures of QOL differ from our study and details of chemotherapy regimes and staging were not available in the absence of case record review²⁷. **A similar pattern of improvement in a range of symptoms and QOL measures in the first year post diagnosis was observed in a cohort study of 285 women with early breast cancer, treated with surgery (just >20% had mastectomy), adjuvant radiotherapy (74%) and systemic therapy in (just >30% of the patients) A similar pattern of improvement over the first year post diagnosis was seen**

in a cohort of women with early breast cancer treated by surgery (just >20% treated by mastectomy) and, where appropriate, adjuvant radiotherapy and systemic therapy using the EORTC QLQ-C 30, Profile of Mood States (POMS), Psychological Adjustment to Illness Scale (PAIS), the Impact of Event Scale (IES) and Fatigue Symptom Inventory²⁹.

Finally, ~~in accordance with other breast cancer QOL studies~~ we observed that younger women reported worse body image (if under 45) and anxiety problems (if under 70 years). This finding is supported by other breast cancer QOL studies, is concordant with clinical experience and emphasises the need for targeted psychological interventions in those women^{11,30}. Younger women also reported higher general pain scores which. ~~The reasons for this are not clear. did not improve with time, and this was not related to the use of aromatase inhibitors (data not shown). The reasons for this are not clear.~~ Persistent pain following breast surgery (breast conserving or mastectomy) was reported by half of the patients in a population-based prospective study of over 3000 patients. The pain was commoner after adjuvant radiotherapy and in younger women.²⁶ The same finding was also reported in a randomised trial of radiotherapy after breast conserving therapy ~~and in a population-based prospective study of more than 3000 patients following breast cancer surgery~~^{13,26}. In the latter study, half the patients experienced moderate to severe pain, consistent with the range of reported pain in the literature from 25%–60%. The wide variation in reports (25%–60%), as the authors suggest, may relate to varying definitions of pain, different methods of pain assessment and mix of surgery and adjuvant therapy. There is insufficient evidence to draw conclusions on each of the treatment-related risk factors for pain.

~~Reassuringly all symptoms and QOL scores improved over time. General pain is the only exception, and this was not related to the use of aromatase inhibitors (data not shown). There is evidence of persistent pain in early breast cancer patients post-surgery, and our findings confirm these observations and call for better recognition of this problem in order to implement screening and patient support. The scores on sexual functioning and sexual enjoyment indicated that the majority of the patients were not sexually active, without between group differences. These observations are consistent with other reports.~~

Several strengths of SUPREMO ~~trial~~ QOL substudy should be mentioned. It is the largest post-mastectomy study which is investigating a well-defined large population of patients treated by mastectomy, which was ~~and was~~ representative of women with early 'intermediate-risk' breast cancer in the UK. Individuals in the QOL study were recruited from almost all UK sites. Only 10 out of 111 sites did not recruit any of their ~~–66 patients, a relatively small number of centres and unlikely to have an impact. We do not know the reasons for the low consent rates in some centres, but it may be related to availability of local resources (dedicated clinical research nurses). This was a large pragmatic study and resources were not available to monitor closely consent rates by centre or to provide extra support.~~

The QOL study was multi-centre from all across the UK sites, representing a wide geographical range, thus minimising participating centre bias. The pre-specified QOL sample size was achieved and exceeded, strengthening our ~~the~~ confidence in the findings. The trial was sufficiently large to allow explorative evaluation of the effects of age and multi-modality treatments. High levels of adherence to questionnaire completion over time were attained (>70%). In addition, guidelines on surgery, radiotherapy and systemic therapy were standardised in the protocol, so any variations in these treatment modalities between treatment arms are unlikely to influence the results.

~~As all patients were randomised following mastectomy, the main limitation of the QOL sub-study~~ substudy is not having a true pre-treatment baseline QOL assessment, as all patients were randomised following mastectomy. The relatively low QOL scores at the time of randomisation may be explained by the recent breast cancer diagnosis and the surgical procedure, and the subsequent improvement in almost all scores, is to be expected. We did not record QOL scores during or shortly after the allocated radiotherapy treatment, so any differences in acute symptoms between the

~~groups, which may predict later toxicity, have not been captured.~~ In addition, since the main trial is ongoing and the loco-regional control and survival status of the patients in the QoL ~~sub-study~~ ~~substudy~~ are not known to us, it is possible patients who had relapsed or died may have had different patterns of QOL.

~~A larger proportion of participants in the QOL study received the dose fractionation schedule as 40 Gy in 15 fractions (69%) compared to 52% in the main trial, where a larger proportion of 27% received 50 Gy in 25 fractions. This difference reflects the variations between the standard practice in UK and EORTC centres at the time of the trial.~~

~~At this 2-year analysis we have not evaluated any effect of fractionation on the QOL outcomes. However, as the clinical significance of the increased chest wall symptoms in the radiotherapy group at 2 years may be relatively limited, we do not expect a major clinical impact of fractionation at this early time point. We expect that the difference in symptoms reported by patients between no radiotherapy and 40-50 Gy will be larger than any difference observed between fractionation schedules. The influence of radiation dose fractionation and technique and the radiation dose parameters to organs at risk will be the subject of a more detailed analysis to be performed in the irradiated group, including evaluation of toxicity (physician scoring). The results will be reported in a separate publication, focusing on the specific technical aspects of the radiotherapy.~~

This paper presents a pre-planned analysis at 2 years post randomisation, with the main QOL analysis being planned at 5 years and QOL data to be collected for 10 years to capture late adverse events. Clearly our results are preliminary and we are therefore cautious in our interpretation. However, it is reassuring that the loco-regional symptoms are minimal and do not impair global QOL and diminish over the initial 2 years of follow up. While it might be argued that analysing QOL at 2 years is too premature, this was a pre-planned analysis. We considered it appropriate to identify any potential early signals of a significant impact on QOL in the absence of a definite oncological outcome. If severe QoL effects were to be identified early, then this would be relevant for clinical decision making in the absence of information on long-term survival benefit. The recent North American guidelines on postmastectomy radiotherapy⁷ emphasise the importance of shared decision making between physician and patient in weighing up the benefits and toxicity of treatment in patients with 1- 3 positive node undergoing axillary node clearance. Information on the impact of PMRT on QOL may help inform this decision-making process, even before the main trial outcomes become available. Further analyses will be reported at 5 and 10 years to determine if the trends at 2 years are sustained. It is possible that late radiotherapy toxicity not seen within the first two years (such as progressive chest wall fibrosis or increased cardiac toxicity due to the combination of radiotherapy and anthracycline-based chemotherapy) may be detected on longer term follow-up and should be captured in our 5 and 10 year analyses. However, we recognise that late cardiac toxicity from radiotherapy may occur beyond 10 years.

~~Further evidence is needed to comment usefully on the impact of radiotherapy on breast reconstruction. We already have the data on immediate reconstruction with a small number of procedures, but we are collecting further information on delayed (beyond 2 years) reconstruction, which will provide valuable general information on rates of breast reconstruction across the UK as well as its impact on patients' experiences and satisfaction with body image.~~

The impact on PMRT on 10-year survival, the primary end-point of the main SUPREMO trial, will not be known before 2023. In the meantime, the decision to administer or omit PMRT can be considered 'preference sensitive' for patients in the SUPREMO trial risk category of 1-3 positive lymph nodes, as both options are legitimate. The patients will be in a better position to make a value judgment on what they consider relevant for them, given the data on various QOL domains presented in this report. Both physicians and patients may thus be helped when weighing up the individual estimates of possible benefits of radiotherapy against the impact of PMRT on toxicity and quality of life QOL

endpoints. ~~This will support the application of informed shared decision making, as recommended by the recent North American guidelines, even before the main trial outcome becomes available⁷.~~

In conclusion, chest wall radiotherapy led to more chest wall symptoms up to 2 years post-randomisation, ~~but the difference is small and unlikely to be clinically significant. There was the difference is small and unlikely to be clinically significant. There was no impact on the other pre-specified QOL domains.~~ However, the trend for worse QOL scores for anxiety, body image and chest-wall symptoms in ~~However, the worse QOL in~~ younger women irrespective of irradiation warrants further investigation. Longer term follow-up at 5 and 10 years will be needed to see if these early trends in quality of life are sustained.

Contributors

GV LW SW JMD IHK NSR were involved in the study design. IHK NSR oversaw the trial and GV LW SW JMD were members of the trial management group. JMD JL MH JC IHK NSR recruited patients. LW GV SW IHK NSR did the data analysis. GV SW JMD JL MH JC IHK NSR interpreted the data. GV LW SW IHK NSR wrote the paper. JMD JL MH JC reviewed the drafts. GV IHK NSR gave final approval of the manuscript.

Declarations of interest

GV has received research grants from National Institute of Health Research (NIHR), Cancer Research UK, Yorkshire Cancer Research and personal fees from Roche, Novartis, and Eisai. SW has received research grant from NIHR. JMD has received personal fees from Pfizer. IHK has received research funding from NIHR. NSR has received research grants from the Dutch Cancer Society and EORTC. The other authors declare no competing interests.

Acknowledgments

We thank the patients, their relatives and treating clinicians, and the hospitals who agreed to participate in this study. The list of contributors from UK participating centres is provided in an online appendix.

We thank Medical Research Council (MRC)(EME 09/800/31), European Organisation for Research and Treatment of Cancer (EORTC), Cancer Australia, The Dutch Cancer Society, the Trustees of the Hong Kong and Shanghai Banking Corporation (HSBC) for funding the study.

We wish to acknowledge the support of the staff at The Information and Statistical Division at National Services Scotland and specifically Kathleen Riddle Principal Trial Manager, Penny Hopwood (The Christie Hospital, Manchester) initial chief Investigator for the QOL ~~sub-study~~substudy (who has subsequently retired), the Scottish Cancer Trials Breast Group under whose auspices the trial was run (Chair: Dr Iain MacPherson), the Trial Management Group, the Trial Steering Committee (Chair Professor Barry Hancock, University of Sheffield), and the Data Monitoring and Ethical Committee (Chair Professor Chris Frost, London School of Hygiene and Tropical Medicine).

We also thank the National Institute for Health Research Cancer Research Networks in England and their equivalent NHS R&D-funded networks in Scotland, Wales, and Northern Ireland for “in-kind” support.

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Tables

Table 1. Patients' demographic and clinical characteristics

<i>Patient demographic and clinical characteristics</i>	QOL study		Full trial	
	No RT	RT	No RT	RT
Demographic	476	471	835	853
Age (mean and SD)	56.3 (11.3)	55.8 (10.8)	55.9 (11.2)	55.8 (11.3)
Menopausal status (number, %)				
Pre-menopausal	126 (26.5)	135 (28.7)	246 (29.5)	243 (28.5)
Peri-menopausal	43 (9.0)	52 (11.0)	68 (8.1)	85 (10.0)
Post-menopausal	290 (60.9)	268 (56.9)	483 (57.8)	475 (55.7)
Not known	17 (3.6)	16 (3.4)	38 (4.6)	50 (5.9)
Tumour characteristics				
Side of primary tumour (number, %)				
Left	238 (51.2)	216 (47.8)	398 (50.1)	407 (51.3)
Right	227 (48.8)	236 (52.2)	396 (49.9)	387 (48.7)
Tumour size (number, %)				
≤2cm	132 (27.7)	138 (29.3)	249 (29.8)	261 (30.6)
2.1-5 cm	337 (70.8)	332 (70.5)	566 (67.8)	566 (66.4)
>5 cm	5 (1.1)	1 (0.2)	4 (0.5)	4 (0.5)
Unknown	2 (0.4)	0	16 (1.9)	22 (2.6)
Tumour grade (number, %)				
I	20 (4.2)	23 (4.9)	46 (5.5)	57 (6.7)
II	190 (39.9)	195 (41.4)	335 (40.1)	333 (39.0)
III	262 (55.0)	250 (53.1)	432 (51.7)	432 (50.6)
Not specified	4 (0.8)	3 (0.6)	22 (2.6)	31 (3.6)
Histological type (number, %)				
Ductal	372 (78.5)	374 (79.4)	641 (78.2)	661 (79.5)
Lobular	58 (12.2)	49 (10.4)	95 (11.6)	89 (10.7)
Mucinous	5 (1.1)	1 (0.2)	7 (0.9)	1 (0.1)
Tubular	1 (0.2)	3 (0.6)	4 (0.5)	4 (0.5)
Adenocarcinoma	3 (0.6)	5 (1.1)	16 (2.0)	13 (1.6)
Other	35 (7.4)	39 (8.3)	57 (7.0)	63 (7.6)
Molecular markers – (number, %)				
ER+/PR+	218 (46.8)	217 (46.7)	417 (51.5)	416 (50.6)
ER+/PR-	48 (10.3)	48 (10.3)	83 (10.3)	99 (12.0)
ER-/PR+	5 (1.1)	0 (0)	8 (1.0)	3 (0.4)
ER-/PR-	87 (18.7)	93 (20.0)	156 (19.3)	162 (19.7)
ER+/PR unknown	96 (20.6)	100 (21.5)	131 (16.2)	132 (16.0)
ER-/PR unknown	12 (2.6)	7 (1.5)	15 (1.9)	11 (1.3)
Her2 positive	140 (29.7)	145(31.1)	273 (33.5)	269 (32.5)
Her2 negative	286 (60.7)	281 (60.2)	475 (58.2)	469 (59.9)
Not measured	45 (9.6)	41 (8.8)	68 (8.3)	63 (7.6)

Patient demographic and clinical characteristics	QOL study		Full trial	
	No RT	RT	No RT	RT
Axillary Nodes (number, %)				
0 (negative)	130 (27.3)	113 (24.0)	219 (26.2)	212 (24.9)
1-	180 (37.8)	199 (42.3)	316 (37.8)	338 (39.6)
2-	101 (21.2)	111 (23.6)	178 (21.3)	194 (22.7)
3-	63 (13.4)	48 (10.2)	107 (12.8)	88 (10.3)
Not known	2 (0.4)	0	15 (1.8)	21 (2.5)
Treatment				
Breast Surgery (number, %)				
Mastectomy only	371 (77.9)	359 (76.2)	653 (78.2)	669 (78.4)
Immediate breast reconstruction prior to RT	50 (10.5)	61 (13.0)	85 (10.2)	97 (11.4)
Late breast reconstruction	55 (11.6)	51 (10.8)	97 (11.6)	87 (10.2)
Axillary surgery (number, %)				
SLN / node sampling	131 (27.9)	108 (22.9)	207 (25.5)	189 (22.8)
SLN plus ANC (Axillary node clearance)	138 (29.4)	124 (26.3)	229 (28.2)	224 (27.0)
ANC (without SLN)	201 (42.8)	239 (50.7)	377 (46.4)	417 (50.2)
Systemic treatment (number Yes, %)				
Neo-adjuvant chemotherapy ¹	1/173 (0.58)	7/173 (4.1)	7/243 (2.9)	16/269 (6.0)
Adjuvant chemotherapy	395/476	401/471	682/835	709/853
Anthracyclines	(83.0)	(85.1)	(81.7)	(83.1)
Taxanes	372/395(94.2)	379/401(94.5)	636/682(93.3)	655/709(92.4)
Trastuzumab	197/395(49.9)	207/401(51.6)	392/682(57.5)	418/709(59.0)
	91/454 (20.5)	92/460 (20.0)	150/782(19.2)	166/806(20.6)
Endocrine therapy (number Yes, %)				
Neo-adjuvant				
Adjuvant	2/200 (1.0)	8/206 (3.9)	10/288 (3.5)	17/316 (5.4)
Aromatase inhibitor	349 (73.3)	363 (77.1)	598 (71.6)	631 (73.9)
Tamoxifen	173/349(49.6)	195/363(53.7)	275/598(46.0)	314/631(49.8)
Other	174/349(49.9)	168/363(46.3)	319/598(53.3)	314/631(49.8)
	2/349 (0.6)	0/363 (0)	4/598 (0.8)	3/631 (0.5)

¹ Only recorded in protocol v29 onwards; the denominator is the total number of recorded chemotherapy treatments from protocol v29 onwards

ER- estrogen receptor; PR – progesteron receptor; SLN- sentinel lymph node(s) procedure; ANC – axillary node clearance

Table 2. Quality of Life (QOL) scores (Standard Deviations, SD) at baseline, year 1 and year 2 follow-up

QoL measure	Baseline		Year 1		Year 2	
Mean (SD)	No RT (n=476)	RT (n=471)	No RT (n=388)	RT (n=388)	No RT (n=350)	RT (n=367)
Age at randomisation	56.3 (11.3)	55.8 (10.8)	56.5 (10.9)	56.1 (10.4)	56.8 (10.9)	56.1 (10.4)
Primary endpoints						
<i>EORTC QLQ-C30</i>						
Global Health/QoL*	60.9 (21.6)	60.4 (20.8)	70.0 (20.5)	70.0 (19.8)	70.2 (20.5)	71.8 (20.1)
Fatigue**	41.6 (25.2)	43.0 (26.1)	30.3 (23.2)	31.0 (24.1)	29.2 (24.2)	27.5 (23.8)
Physical Functioning*	79.6 (20.2)	80.1 (19.6)	81.9 (19.0)	81.1 (19.1)	82.0 (18.6)	82.1 (19.3)
<i>EORTC QLQ-BR23</i>						
Arm symptoms**	20.3 (20.5)	21.2 (21.7)	21.2 (21.7)	22.4 (22.0)	20.7 (21.4)	19.9 (20.3)
Chest wall/breast symptoms**	17.3 (17.0)	18.1 (18.3)	13.1 (16.3)	16.1 (16.7)	11.6 (14.6)	14.1 (15.8)
<i>Body Image Scale**</i>	10.3 (7.9)	11.1 (8.2)	9.3 (7.6)	9.8 (7.7)	8.1 (6.7)	8.7 (7.4)
<i>Hospital Anxiety and Depression Scale (HADS)</i>						
Anxiety	6.2 (4.4)	6.1 (4.3)	6.8 (4.7)	6.5 (4.4)	6.3 (4.3)	6.5 (4.4)
Depression	4.5 (3.7)	4.6 (3.7)	4.2 (3.7)	4.2 (3.8)	4.0 (3.5)	4.2 (3.9)
Secondary endpoints						
<i>EORTC QLQ-C30</i>						
Role Functioning *	65.2 (30.9)	63.0 (30.5)	79.3 (27.1)	78.8 (25.8)	79.7 (27.6)	81.0 (26.9)
Social Functioning *	65.5 (28.7)	64.0 (29.1)	79.4 (25.6)	80.3 (24.7)	80.5 (26.1)	83.9 (25.2)
Pain**	22.6 (26.5)	24.8 (27.9)	21.7 (26.8)	23.7 (26.5)	23.4 (27.3)	21.6 (25.9)
Nausea Vomiting**	11.2 (17.6)	11.5 (20.1)	5.3 (13.1)	5.1 (12.1)	4.6 (12.2)	5.1 (13.6)
<i>EORTC QLQ-BR23</i>						
Sexual Functioning*	11.5 (18.1) n=455	12.5 (19.0) n=459	15.7 (20.5) n=372	17.6 (21.2) n=374	16.3 (21.7) n=325	18.1 (22.3) n=353
Exploratory variables						
<i>EORTC QLQ-C30</i>						
Emotional Functioning*	74.7 (22.6)	73.7 (24.4)	75.2 (23.6)	75.2 (22.3)	77.3 (22.5)	75.7 (23.3)
Cognitive Functioning*	77.1 (23.4)	75.0 (26.1)	78.2 (22.8)	78.2 (22.9)	78.6 (22.8)	78.2 (23.8)
Dyspnoea**	20.8 (26.4)	20.0 (26.1)	14.6 (23.5)	14.8 (23.0)	14.3 (23.2)	13.4 (22.5)

QoL measure	Baseline		Year 1		Year 2	
Mean (SD)	No RT (n=476)	RT (n=471)	No RT (n=388)	RT (n=388)	No RT (n=350)	RT (n=367)
Insomnia**	36.3 (31.1)	37.2 (32.8)	36.4 (33.5)	38.5 (32.8)	33.9 (31.9)	35.0 (30.5)
Appetite loss**	20.7 (28.9)	19.2 (27.9)	9.5 (19.8)	8.7 (18.5)	9.1 (19.9)	9.0 (20.7)
Constipation**	18.2 (26.3)	17.0 (26.1)	14.9 (24.5)	14.5 (24.1)	17.6 (27.7)	14.5 (24.3)
Diarrhoea**	11.9 (20.7)	12.1 (23.8)	7.6 (17.5)	8.4 (18.7)	5.4 (15.1)	8.7 (19.1)
Financial difficulties**	23.9 (33.1)	23.2 (31.7)	15.8 (28.5)	17.1 (27.8)	14.1 (27.0)	13.8 (26.6)
<i>EORTC QLQ-BR23</i>						
Sexual enjoyment*	49.9 (26.9) n=121	53.0 (29.1) n=132	54.4 (28.3) n=136	56.5 (26.5) n=144	52.5 (26.1) n=115	56.6 (28.8) n=136
Future perspective**	45.8 (31.2)	46.4 (32.8)	49.8 (32.3)	50.9 (31.6)	54.4 (30.1)	54.1 (30.9)
Systemic therapy side-effects**	34.8 (23.1)	35.2 (22.7)	19.3 (15.2)	19.6 (15.6)	18.6 (14.9)	18.3 (15.0)
Hair loss**	29.6 (37.5)	31.7 (39.3)	6.2 (20.4)	6.4 (21.8)	3.8 (20.7)	4.9 (17.1)
EQ-5D-3L***	0.74 (0.22)	0.74 (0.22)	0.75 (0.25)	0.75 (0.24)	0.76 (0.24)	0.77 (0.22)

*EORTC QLQ-C30 Functional scores- range 0-100 (higher score = good functioning)

** EORTC QLQ-C30 Symptom scores – range 0-100 (higher score = worse symptoms)

*** EQ-5D-3L score-range 0-1.

Table 3. Mixed effects models (fixed effects) for the primary QOL outcomes

Outcome	Model variable	Estimate of effects	95% CI	p
Global QOL (C30)	Baseline score	-0.57	-0.63, -0.52	<0.0001
	Age- ref* >70	-	-	-
	- <45	1.12	-3.45, 5.78	0.64
	- 45-54	3.25	-0.62, 7.12	0.10
	- 55-69	3.54	-0.28, 7.36	0.0697
	Visit-ref year1	0.75	-0.46, 1.97	0.23
	RT –ref no RT	1.39	-0.92, 3.71	0.24
		Adjusted mean of 'change scores'***	95% CI	p-value***
	RT	8.63	6.86, 10.40	<0.0001
	No RT	7.23	5.46, 9.01	<0.0001
Fatigue (C30)	Baseline score	-0.59	-0.65, -0.54	<0.0001
	Age- ref >70	-	-	-
	- <45	-2.41	-8.07, 3.26	0.40
	- 45-54	-4.14	-8.84, 0.56	0.0798
	- 55-69	-3.13	-7.73, 1.47	0.18
	Visit-ref year1	-1.83	-3.20, -0.46	0.0094
	Immediate reconstruction	5.32	0.94, 9.69	0.017
	Ref no recon			0.17
	RT –ref no RT	-1.93	-4.70, 0.84	
	RT	-9.54	-12.19, -6.89	<0.0001
	No RT	-7.61	-10.35, -4.87	<0.0001
Physical function (C30)	Baseline score	-0.41	-0.46, -0.35	<0.0001
	Age- ref >70	-	-	-
	- <45	7.91	3.94, 11.87	<0.0001
	- 45-54	7.06	3.80, 10.32	<0.0001
	- 55-69	4.29	1.06, 7.51	0.0092
	Visit-ref year1	0.20	-0.68, 1.08	0.65
	RT –ref no RT	-0.17	-2.13, 1.79	0.87
	RT	-0.02	-1.53, 1.48	0.97
	No RT	0.14	-1.36, 1.65	0.85
Chest wall symptoms (BR23)	Baseline score	-0.57	-0.62, -0.52	<0.0001
	Age- ref >70	-	-	-
	- <45	4.49	0.59, 8.39	0.022
	- 45-54	1.88	-1.46, 5.22	0.26
	- 55-69	2.36	-0.79, 5.51	0.14
	Visit-ref year1	-1.34	-2.36, -0.31	0.010
	Chemo-ref no chemo	3.74	0.87, 6.61	0.011
	RT –ref no RT	2.17	0.40, 3.94	0.016
	RT	-3.13	-4.74, -1.51	0.0002
	No RT	-5.30	-6.88, -3.71	<0.0001

Arm and shoulder symptoms (BR23)	Baseline score	-0.51	-0.57, 0.45	<0.0001
	Age- ref >70	-	-	-
	- <45	0.86	-4.42, 6.14	0.74
	- 45-54	2.89	-1.64, 7.41	0.21
	- 55-69	2.76	-1.51, 7.03	0.20
	Visit-ref year1	-0.93	-2.22, 0.37	0.16
	Chemo-ref no chemo	6.15	2.26, 10.05	0.002 ¹
	RT –ref no RT	-0.53	-2.92, 1.86	0.66
	RT	-1.44	-3.63, 0.75	0.19
Body Image Scale	No RT	-0.91	-3.06, 1.24	0.40
	Baseline score	-0.39	-0.43, 0.34	<0.0001
	Age- ref >70	-	-	-
	<45	1.96	0.53, 3.39	0.007 ⁴
	45-54	1.39	0.20, 2.58	0.022
	55-69	0.83	-0.33, 1.99	0.15
	Visit-ref year1	-0.91	-1.28, -0.55	<0.0001
	RT –ref no RT	-0.09	-0.79, 0.61	0.79
	RT	-1.36	-1.90, -0.83	<0.0001
HADS-Anxiety	No RT	-1.27	-1.81, -0.73	<0.0001
	Baseline score	-0.30	-0.35, -0.25	<0.0001
	Age- ref >70	-	-	-
	- <45	1.69	0.86, 2.53	<0.0001
	- 45-54	1.36	0.67, 2.06	≤0.0001
	- 55-69	1.21	0.53, 1.90	0.0005 ⁰
	Visit-ref year1	-0.05	-0.29, 0.18	0.66
	RT –ref no RT	-0.16	-0.57, 0.25	0.44
	RT	0.44	0.13, 0.76	0.006 ¹
HADS-Depression	No RT	0.60	0.29, 0.92	0.0002 ²
	Baseline score	-0.35	-0.41, 0.30	<0.0001
	Age- ref >70	-	-	-
	- <45	0.07	-0.73, 0.87	0.87
	- 45-54	-0.05	-0.72, 0.61	0.88
	- 55-69	-0.04	-0.69, 0.62	0.91
	Visit-ref year1	0.02	-0.16, 0.20	0.94
	RT –ref no RT	-0.14	0.54, 0.25	0.48
	RT	-0.19	-0.50, 0.11	0.21
Pain (C30)	No RT	0.05	-0.35, 0.25	0.75
	Baseline score	-0.51	-0.57, -0.46	<0.0001
	Age- ref >70	-	-	-
	- <45	-0.18	-6.16, 5.80	0.95
	- 45-54	2.76	-2.17, 7.69	0.27
	- 55-69	2.18	-2.70, 7.06	0.38
	Visit-ref year1	0.31	-1.29, 1.91	0.70
	RT –ref no RT	-0.65	-3.62, 2.33	0.67
	RT	0.28	-1.99, 2.56	0.81
	No RT	0.93	-1.35, 3.20	0.42

* ref =reference category in the mixed-effects models

** the adjusted mean for the individual arms is the mean of the 'change scores', (defined as change from baseline to year 1 and from baseline to year 2) in each of the treatment groups, adjusted for baseline score, visit, and age;

***p values - whether each of the means of the 'change scores' within each individual arm is significantly different from zero (i.e., improvement or deterioration in scores from baseline)

Responses are in bold. Page numbers below refer to the TRACKED version of the manuscript. Page numbers in the CONSORT checklist refer to the CLEAN version.

Editorial comments:

1. Regarding reviewer 1, comment 2 (re: details about/influence of radiotherapy technique): please summarise your response to this point about the influence of the radiotherapy technique and add to the Discussion. Please also state that the results of your more detailed pre-planned analysis of the irradiated group will be reported in a separate publication.

The following paragraph has been added to the Discussion, Page 13

At this 2-year analysis we have not evaluated any effect of fractionation on the QOL outcomes. However, as the clinical significance of the increased chest wall symptoms in the radiotherapy group at 2 years may be relatively limited, we do not expect a major clinical impact of fractionation at this early time point. We expect that the difference in symptoms reported by patients between no radiotherapy and 40-50 Gy will be larger than any difference observed between fractionation schedules. The influence of radiation dose fractionation and technique and the radiation dose parameters to organs at risk will be the subject of a more detailed analysis to be performed in the irradiated group, including evaluation of toxicity (physician scoring). The results will be reported in a separate publication, focusing on the specific technical aspects of the radiotherapy.

2. Regarding reviewer 1, comment 4: please add some text to the Discussion section of your paper acknowledging that because nodal radiotherapy was not given, the findings of your study are not generalizable to women treated with axillary nodal dissection and regional nodal radiotherapy.

The following paragraph has been modified in the Discussion to emphasise the point of the reviewer, page 11

Our findings are not generalisable to women who were treated with both an axillary nodal dissection and regional nodal radiotherapy. This treatment is generally reserved for patients with higher nodal load (N2 and N3 disease) than included in the SUPREMO trial (pN0 or pN1).

3. Regarding reviewer 1, comment 6: please mention in the Discussion that you do not have power to evaluate between-group differences taking into account the type of reconstruction. Please also briefly mention the Alliance for Clinical Trials in Oncology NCT03414970 trial in the Discussion, including details about the trial (its primary endpoint, its status, and when it will complete).

The following paragraph has been added to the Discussion, page 12

Due to the low rates of reconstruction in SUPREMO, we do not have the power to assess between group differences taking into account the dose schedules in the radiotherapy group. A direct comparison of conventional versus hypo-fractionation for chest wall radiotherapy after breast reconstruction is being carried out in North America by the Alliance for Clinical Trials in Oncology (NCT03414970). The primary objective is to evaluate whether the reconstruction complication rate at 24 months post radiation is non-inferior with hypofractionation. The trial is ongoing and will complete recruitment in 2021, with final results in August 2025.

4. Regarding reviewer 2, major comment 2: please add some additional text to your paper to justify your specific reasons for publishing these results at 2 years.

The following paragraph has been added to the Discussion, page 14

While it might be argued that analysing QOL at 2 years is too premature, this was a pre-planned analysis. We considered it appropriate to identify any potential early signals of a significant impact on QOL in the absence of a definite oncological outcome. If severe QoL effects were to be identified early, then this would be relevant for clinical decision making in the absence of information on long-term survival benefit. The recent North American guidelines on postmastectomy radiotherapy⁷ emphasise the importance of shared decision making between physician and patient in weighing up the benefits and toxicity of treatment in patients with 1- 3 positive node undergoing axillary node clearance. Information on the impact of PMRT on QOL may help inform this decision-making process, even before the main trial outcomes become available.

5. Regarding reviewer 2, major comment 3: please add some text to the Discussion explaining that you have decided not to include the details of radiotherapy technique in the current analyses, and that the results of your more detailed pre-planned analysis of the irradiated group will be reported in a separate publication.

This issue is the same as point 1 above and has been addressed in the Discussion, Page 13.

At this 2-year analysis we have not evaluated any effect of fractionation on the QOL outcomes. However, as the clinical significance of the increased chest wall symptoms in the radiotherapy group at 2 years may be relatively limited, we do not expect a major clinical impact of fractionation at this early time point. We expect that the difference in symptoms reported by patients between no radiotherapy and 40-50 Gy will be larger than any difference observed between fractionation schedules. The influence of radiation dose fractionation and technique and the radiation dose parameters to organs at risk will be the subject of a more detailed analysis to be performed in the irradiated group, including evaluation of toxicity (physician scoring). The results will be reported in a separate publication, focusing on the specific technical aspects of the radiotherapy.

6. Regarding reviewer 2, major comment 4: please could you add this table of consent rates for the QoL sub-study in the different centres to the web appendix and cite it at an appropriate place in the main text of the Results.

The Table with consent rates has been added to the Web appendix and the following text added to the Results, first paragraph, page 8.

All patients eligible for SUPREMO from 111 UK centres were invited to participate in the QOL sub-study (n=1258). This approach was adopted in order to avoid any bias in selecting centres or patients. The consent rate between centres varied (see Table consent rates in the web appendix, page 1). The majority of the centres (73 centres) had consent rates of 80% or above. Ten centres did not include any of their 66 patients in the QOL study.

7. Also regarding reviewer 2, major comment 4: please add some text to the Discussion about the low consent rates in some centres and the possible reasons why.

The following paragraph has been added to the Discussion, page 12

Only 10 out of 111 sites did not recruit any of their 66 patients, a relatively small number of centres and unlikely to have an impact. We do not know the reasons for the low

consent rates in some centres, but it may be related to availability of local resources (dedicated clinical research nurses). This was a large pragmatic study and resources were not available to monitor closely consent rates by centre or to provide extra support.

8. Regarding reviewer 2, major comment 9: please add some text to the Discussion explaining why you used mean scores for QoL measures (ie, in order to enable comparisons with other published studies).

Added to Discussion, Page 11, first paragraph as part of an extended paragraph on interpretation of the results.

We opted to present the mean scores and standard deviations in order to allow comparisons with other studies.

9. Regarding reviewer 2, major comment 11: please note that we do not use shading in tables; please therefore amend the table footnotes accordingly to avoid referring to shaded cells.

Shading has been removed from Table 3 and the footnote corrected.

10. Also regarding reviewer 2, major comment 11 (p values): Lancet Oncology reporting style is to report p values to 2 significant figures (ie, $p=0.XX$, $p=0.0XX$, $p<0.0XX$ or $p<0.00XX$), unless $p<0.0001$ (if this is the case, then please revise to the latter). It looks like most of the p values in table 3 do conform to this but please check carefully (in table 3 and elsewhere in the paper).

This has been corrected.

11. Also regarding reviewer 2, major comment 11: please ensure that you state clearly in the Methods (statistical analysis section) whether analyses were done by an intention-to-treat basis or otherwise.

Stated on page 8.

12. Regarding reviewer 2, minor comment 1A: please summarise your response to this point about missing data and add to the Methods, Statistical Analysis section.

An explanation has been added on page 7.

When calculating QOL questionnaire or sub-scale scores, we followed official questionnaire guidelines on handling missing individual items. In general, if more than 50% of the items were missing, sub-scale scores were not calculated (missing); if less than 50% of items were missing, those were replaced by the mean of the answered items and a score was calculated. Where no guidance existed, that score was recorded as missing.

13. Regarding reviewer 2, minor comment 6: please summarise your response to this point and add to the Discussion. **Responses to Sexual function items**

More details have been added to the Results section (page 10)

We had good completion rate for the general sexual function questions 97% (914/947) but only 27% (253/914) patients completed the conditional sexual enjoyment questions at baseline suggesting that the vast majority of patients are not sexually active (Table2). These observations are consistent with other reports.

Initially we mentioned this observation in the discussion. But subsequently decided to remove it, as it does not belong to any existing section, we don't have space to add references to make the discussion more meaningful.

14. Regarding reviewer 3, comment 2: please add some text to the Discussion explaining that there is not currently any available data or guidance on what difference in the sub-scale scores of EORTC-BR23 is clinically significant (and that such definitions only exist for the EORTC QLQ-C30).

Added to Discussion, Page 10, first paragraph as part of an extended paragraph on interpretation of the results. After the previous re-submission, we did additional descriptive analysis of the 'change score' for chest wall symptoms in an attempt to understand if this statistically significant difference is clinically meaningful. We followed FDA guidance on using 'responder analysis' at the individual level. This analysis has been added to the Web appendix, and an extended paragraph describing an alternative interpretation of the observed difference added to the Discussion.

The estimated effect is small, with a difference in 'change scores' between the radiotherapy and control group of 2.17 points; 95% CI 0.40, 3.94. There is published data on EORTC QLQ-C30 on 'change scores' within groups or 'scores difference' between groups that is clinically significant, but to the best of our knowledge, there is no such available data on EORTC-BR23 scores²³. We opted to present the mean scores and standard deviations in order to allow comparisons with other studies. In an attempt to explore the clinical significance of the observed statistically significant difference, we looked at using a generic approach of 0.5 of the standard deviation to indicate minimally important difference. Therefore, we calculated the standard deviation of the 'change score' for chest wall symptoms from baseline to year 1 in the control group.²⁴ The standard deviation was 17.3 and a score 8.65 is likely to indicate a clinically meaningful difference. The observed difference of 2.17 is relatively small and unlikely to be of clinical significance, which is of course reassuring for patients and clinicians. Recent guidelines from Federal Drugs Administration (FDA) recommend establishing a meaningful change in patient reported outcomes measures at the individual level (i.e., defining a responder) versus at the treatment group level²⁵. The definition of a responder being "a score change in a measure, experienced by an individual patient over a predetermined time period that has been demonstrated in the target population to have a significant treatment benefit". Using this approach and a 'change score' of 8.65 as a cut-off score for clinical significance we applied 'responder analysis' (web appendix page 7). We calculated proportions of patients whose scores 'improved' by < -8.65 points between baseline and year 1, those who remained 'stable'/no change' (change score= ± 8.65) and those whose scores 'worsened' by $> +8.65$ points. This 'responder analysis' showed that 16.3% (63/386) of patients receiving radiotherapy reported clinically meaningful worse 'change score' vs 11.9% (46/385) of those without radiotherapy. In other words, 4.4% more patients on radiotherapy experience worse chest wall symptoms than those not receiving PMRT. This way of interpretation of results may be more informative to clinicians and patients, but a note of caution is appropriate due to the assumptions described above.

15. Regarding reviewer 4, comment 3: please add some text to the Discussion explain that the number of neo-adjuvantly treated patients is too small to do a subgroup analysis of these patients.

A sentence has been added to the Discussion page 11.

Neo-adjuvant treatment was allowed in a later protocol version (version 29), but the number of treated patients is too small (n=8) for valid conclusions and therefore we did not perform any between group comparisons.

16. Regarding reviewer 5, comment 1: please acknowledge this point in the Discussion.
Done, the added text is the same as point 4 above, Page 12 in Discussion.

17. Regarding reviewer 5, comment 2: please could you add this analysis of the extent of nodal surgery on the scores to the web appendix and cite it in the Results section in the main paper.

The analysis on the extent of axillary surgery has been added in the Web appendix and the section in the Results extended to include all observations.

Contrary to the clinical expectations, the extent of axillary surgery (comparison of 3 types: 1) sentinel node biopsy or node sampling; 2) sentinel node biopsy plus axillary node clearance; 3) axillary node clearance) did not have an effect on arm/shoulder symptoms scores (see Web appendix, page 3). Furthermore, the extent of axillary surgery did not have an impact on any of the pre-specified QOL variables, except a trend for higher HADS-Anxiety in patients with sentinel node biopsy plus axillary node clearance.

18. Please check with your co-authors, and confirm, that all names are spelt correctly, and affiliations listed correctly. We cannot guarantee that we will be able to correct names and affiliations after publication of your article.

This has been done and one correction made Linda Jane Williams

19. Please indicate in the authorship if any authors are full professors.

Done

20. Please give full first names for all authors (unless 'J Michael Dixon' prefers to be listed as such, in which case please confirm).

I confirm that Professor J Michael Dixon prefers to be listed as above.

21. Please ensure that your Research in Context panel is structured as follows and contains the following important details in each section:

Evidence before this study

This section should include a description of all the evidence that the authors considered before undertaking this study. Authors should briefly state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including any date restrictions of the search, ie, articles published between month/day/year and month/day/year), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.

Added value of this study

Authors should describe here how their findings add value to the existing evidence.

Implications of all the available evidence

Authors should state the implications for practice or policy and future research of their study combined with existing evidence.

We confirm that the above structure has been followed.

22. Summary: Your abstract should conform to the CONSORT guidelines for abstracts (CONSORT for Abstracts: Lancet 2008; 371: 281-83), and must include:

- a) Methods: A brief summary of the main patient characteristics (ie, main entry criteria)
- b) Methods: Details of the regimens used.
- c) Methods: Details of how randomisation was done (eg, allocation concealment; nature of blinding, if any; how sequence was generated; stratification factors, etc).
- d) Methods: An explicit description of the actual primary endpoint.
- e) Methods: The nature by which analyses were done (eg, intention to treat, per protocol).
- f) Methods: The trial registration number.
- g) Methods: The status of the trial - is it ongoing/still enrolling/is this an interim analysis, etc?
- h) Findings: Data for the primary endpoint only.
- i) Findings: The most common (grade 3-4) adverse events for all treatment groups (incl actual numbers of patients affected); any serious adverse events. Any treatment-related deaths (number and cause).
- j) Interpretation: please do not just restate your findings. What do they mean, clinically? What are their implications?

See recent issues of the journal for examples. Accuracy and completeness here are essential.

We confirm that the above information has been provided.

23. Please confirm that your study conforms to the CONSORT guidelines by completing and returning the checklist.

We confirm that our study conforms to CONSOT guidelines, we are submitting the completed checklist.

CONSORT - for RCTs - <http://download.thelancet.com/flatcontentassets/authors/tlo-consort-checklist.pdf>

24. Please ensure your methods section is structured using the following subheadings in this order: Study design and participants; Randomisation and masking; Procedures; Outcomes; Statistical analysis.

We confirm that the above subheadings are used to structure the Methods section.

25. Methods, Study design and participants. Please ensure that the following items are included:

- a) Age limit for eligibility.
- b) Indicate the means of disease evaluation (eg, RECIST, etc)
- c) Permitted performance status(es) defined.
- d) An indication of estimated life expectancy of eligible patients.
- e) Laboratory tests required to assess eligibility.
- f) Previous treatments permitted/not permitted (and washout period(s)).
- g) If the trial is second-line (or above), mention criteria for determining progression at inclusion.
- h) Comorbidities permitted/not permitted.
- i) Nature of consent sought and IRB approval.

We confirm the above information has been included

26. Methods: Randomisation and masking. Please include details of:

- a) Sequence generation. A description of the actual method of randomisation (ie, the method used to generate the sequence with which participants are allocated to comparison groups, including details of the methods used to restrict the randomisation—eg, block, stratification). Words and phrases such as "randomised", and "randomly assigned" without qualification are not acceptable.
- b) Allocation concealment. A description of the method used to conceal assignment of a participant without knowledge of the next assignment in the sequence.
- c) Implementation. Who generated the allocation sequence, who enrolled participants, and who assigned them to the trial groups

We confirm this information has been included.

27. Methods: procedures. Please ensure that the following items are included:

- a) Planned doses of treatment(s).
- b) Duration of treatment/number of cycles planned.
- c) Criteria for a patient to be removed from the study.
- d) Details of permitted dose reductions/interruptions.
- e) Type and frequency of radiographic assessments.
- f) If applicable, whether or not the primary endpoint was centrally reviewed.
- g) Frequency and type of laboratory monitoring.
- h) Frequency and type of adverse event monitoring.
- i) If you have included such data for a drug(s), please confirm that the dose, route, and frequency of administration (and the form: eg, a particular salt) are correct.

We confirm this information has been included.

28. Methods: Outcomes: Please ensure the following items are included:

- a) Definition of the primary endpoint for the trial overall and for this QoL substudy.
- b) Definition of all secondary endpoints for this QoL substudy.

These have been added on page 7.

Outcomes

The primary endpoint of SUPREMO trial is 10-year overall survival. Quality of life is a secondary endpoint alongside chest-wall recurrence, regional recurrence, disease free survival, acute and late morbidity and cost-effectiveness. In the QOL sub-study we pre-

specified as primary outcomes global QOL, fatigue, physical function, chest wall symptoms, shoulder and arm symptoms, body image, anxiety and depression. Secondary outcomes are role, social, sexual functioning, pain and nausea/vomiting.

29. Methods: Statistical analysis. Please ensure the following items are included:

- a) Hypothesis, power calculation, and derivation of sample size. *Done*
- b) Definitions of population assessed for primary and secondary outcomes, and for safety (eg, ITT, per protocol, etc).
- c) Rules for defining patients as not assessable.
- d) Statistical methods for analysis of the primary and secondary outcomes.
- e) Any sensitivity analyses, etc.
- f) Any planned interim analyses.
- g) The trial registration number - "This study is registered [as an International Standard Randomised Controlled Trial/with ClinicalTrials.gov/similar], number [ISRCTNxxxxxxxx/NCTxxxxxxxx/similar]."

We confirm all above items are included, except c) rules for defining patients as not assessable (which does not apply to the study).

30. As I am sure you are aware, the Lancet group are very supportive of protocol-based research and so have recently decided to encourage authors to post the protocol document on a publicly accessible website; a margin link to the website will then be put in the paper. Would you like to do this for your protocol? If so, please send us the protocol link with your final corrections. Please note that if you do wish to do this then the weblink should not be temporary. Alternatively, you can place your protocol in the supplementary web appendix.

We have a link to the protocol on the SUPREMO website- <http://www.supremo-trial.com/SUPREMO%20protocol%20version29.pdf>. We are happy for this link to be included in the paper.

31. Please give the exact patient enrolment dates (if known)—ie, day, month, year - day, month, year.

Enrolment dates were from August 4, 2006 till April 29, 2013, we have corrected in the paper.

32. Results: It is Lancet style to give actual numbers (numerator and denominator) together with percentages—eg, '5 (50%) of 10 patients in the treatment group received treatment per protocol'. Please ensure that you have done this throughout the Results section.

This has been checked.

33. Results: Please give median follow-up (and IQR) for the analyses presented.

This information has been added to Results page 8.

Median follow-up for the patients who returned the baseline questionnaires was 748 days (interquartile range 417-763) for the control group and 749 days (interquartile range 725-762) for radiotherapy group.

34. Results: please explicitly state the number of patients included in analyses, and the number of patients deemed ineligible (and reasons why).

The number of patients included in the analysis (n=947) is explicitly stated on page 8.

35. Results: Please do not translate HRs/RRs/ORs into percentages, since this can be misleading. Simply indicate the HRs/ORs/RRs and let the reader interpret the data.

We have not converted any OR into percentages

36. Results: The adverse events table should be stratified by grades 1-2, 3, 4 and 5. For adverse events of grade 1 or 2, any occurring in $\geq 10\%$ of patients should be reported. All grade 3, 4, and 5 events should be reported.

We do not report any adverse events in this manuscript.

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We are uploading the signed statements with the submission for 4 or the 5 named individuals in the acknowledgments section. We were unable to contact Penny Hopwood who has been retired for a few years. We keep trying. We are keen to acknowledge Dr Hopwood as she was the original lead for the QOL substudy, designed the study and wrote the protocol section.

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This list is now provided for all UK centres participating in the QOL substudy

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citation: <https://www.ncbi.nlm.nih.gov/pubmed/27864015>. It should not contain the names of authors of the manuscript that are already listed, only those in the study group.

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Although this was an international trial supported by EORTC and BIG, the data presented in this manuscript has been collected by UK centres only, so we did not consider it relevant to include the international investigators with this publication.

52. Please state whether this study was fully or in part NIH funded and whether any authors are employed by the NIH.

The study was not funded by NIH and none of the authors are employed by NIH.

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- * Numbers in text and tables should always be provided if % is shown.

- * Means should be accompanied by SDs, and medians by interquartile range.

- * Exact p values should be provided, unless $p < 0.0001$

Drug names

- * Recommended international nomenclature (rINN) is required

References

- * Vancouver style (eg, Smith A, Jones, B, Clements S. Clinical transplantation of tissue-engineered airway. Lancet 2008; 372: 1201-09. Hourigan P. Ankle injuries. In: Sports medicine. Chan D, ed. London: Elsevier, 2008: 230-47.)

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Web appendix

[Click here to download Necessary Additional Data: Velikova SUPREMO QOL Web Appendix 16june18.pdf](#)

SUPREMO, an MRC phase III randomised trial to assess the role of adjuvant chest wall irradiation in 'intermediate risk' operable breast cancer following mastectomy

MRC SUPREMO TRIAL (BIG 2-04)

(Selective Use of Postoperative Radiotherapy AftEr MastectOmy)

ISRCTN61145589 MREC Ref:05/S0501/106

under the auspices of:

UK Medical Research Council
Scottish Cancer Trials Breast Group

in association with:

Breast International Group:
Anglo-Celtic Co-operative Oncology Group
Borstkanker Onderzoeksgroep Nederland
Central East European Oncology Group
Chinese Network of 9 Hospitals (under leadership of National Cancer Centre, Academy of Medical Sciences, Beijing)
European Organisation for Research and Treatment of Cancer
GECO Peru
Hellenic Breast Surgical Society
International Breast Cancer Study Group
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Japanese Breast Cancer Research Group
National Cancer Institute of Canada –Cancer Trials Group
National Cancer Research Institute Breast Cancer Studies Group
Swedish Breast Group
Swiss Group for Clinical Cancer Research
Trans-Tasman Radiation Oncology Group

Chief Investigator:
Prof Ian Kunkler
Edinburgh Cancer Centre
Western General Hospital
University of Edinburgh
Edinburgh, Scotland, UK
i.kunkler@ed.ac.uk

Co-chief Investigator:
Dr Peter Canney
Beatson West of Scotland
Cancer Centre
Glasgow, Scotland, UK
peter.canney@ggc.scot.nhs.uk



Final protocol version 29: 30th August 2010

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MRC Supremo protocol version 29– 30th August 2010: part of NCRN portfolio

approved by: Prof Ian Kunkler



Signed.....Date:

Summary

SUPREMO

A randomised phase III trial assessing the role of chest wall irradiation in women with intermediate risk breast cancer following mastectomy.

Eligibility (see Appendix IX for clarification of clinical staging (c), pathological staging (p) and pathological staging following neoadjuvant therapy (yp)).

1.1 Stage II histologically confirmed unilateral breast cancer following mastectomy including the following pTNM stages:

- **pT1N1M0**
- **pT2N1M0**
- **pT2N0M0 if grade III histology and/or lymphovascular invasion**
- **pT3N0M0.**

If the tumour area comprises multiple small adjacent foci of invasive carcinoma then overall maximum dimension is taken to determine the size for T staging (see section 7.2.2 for a more detailed explanation). Multifocal or multicentric tumours can be included (pT1m; pT2m; pT3m). The size of the largest tumour focus determines the T stage classification. See section 7.2.1).

1.2 Stage II histologically confirmed unilateral breast cancer following **neoadjuvant systemic therapy** and mastectomy, if the original clinical stage was cT1-2cN0-1M0 or cT1-2pN1(sn)M0 and with the following (**yp**TNM) stages after neoadjuvant systemic therapy:

- **ypT1pN1M0**
- **ypT2pN1M0**
- **ypT2pN0M0 if grade III histology and/or lymphovascular invasion.**
- **ypT0pN0 or ypT1pN0 or ypT0pN1** (pathological complete remission, or near complete remission).
- **ypT2N0** independent of grade or lymphovascular invasion, if the original clinical stage was cT3N0.

Also:

- **ypT3N0M0**, if original clinical staging was cT1-3cN0 M0 or cT1-3pN0 (sn) M0.

1.3 Unilateral invasive breast cancer that conforms to the initial clinical staging of criterion 1, but has been down-staged by **neoadjuvant** systemic therapy to **ypT0 pN0 or ypT1pN0 or ypT0pN1** (pathological complete remission, or near complete remission). If tumour stage **cT3 or ypT3**, then nodal status must be N0 both before and after neoadjuvant systemic therapy.

2. Undergone total mastectomy (with minimum of 1 mm clear margin of invasive cancer and DCIS) and axillary staging procedure.

3.1 If axillary node positive (1-3 positive nodes [including micrometastases >0.2mm-≤2mm]) then an axillary node clearance (minimum of 8 nodes removed) should have been performed. Isolated tumour cells do not count as micrometastases.

3.2 Axillary node negative status can be determined on the basis of either axillary clearance or axillary node sampling or sentinel node biopsy.

3.3 Sentinel nodes identified in the internal mammary chain are considered pN1b or pN1c if histologically proven. Patients can be included in the trial with microscopic metastasis in the internal mammary chain detected by sentinel node biopsy, if not more than 3 tumour positive nodes in axillary lymph nodes. If not biopsied, internal mammary chain sentinel nodes are considered tumour negative for staging.

3.4 Before neoadjuvant systemic therapy, axillary ultrasound is advised. Abnormal axillary nodes based on imaging (mammogram or ultrasound) should be sampled by guided needle sampling or core biopsy. Where axillary ultrasound is normal, negative axillary node status does not require histological confirmation before starting neoadjuvant systemic therapy. Positive, or negative, nodal status may also be determined by sentinel node biopsy before start of neoadjuvant therapy.

4. Fit for adjuvant or neoadjuvant chemotherapy (if indicated), adjuvant or neoadjuvant endocrine therapy (if indicated) and postoperative irradiation.

5. Written, informed consent.

Additional explanation for the inclusion criteria:

- 1.** Patients undergoing immediate breast reconstruction are eligible for inclusion.
- 2.** Patients who are carriers of known pathological mutations in BRCA1 or BRCA2 genes are eligible for inclusion.
- 3.** Neoadjuvant systemic therapy:
 - 3.1** Patients who have undergone mastectomy after neoadjuvant systemic therapy are eligible for inclusion. For determination of tumour stage and nodal involvement, please see Section 7.3.
 - 3.2** Tumour grade, hormone receptor status and Her-2 receptor status (or HER gene amplification) should be determined on a core biopsy taken before the start of neoadjuvant systemic therapy. Lymphovascular invasion may be assessed on both the core biopsy and post treatment excision.
 - 3.3** T2 tumours that are cN0 and remain ypN0 after neoadjuvant systemic therapy can only be included if grade III histology and / or lymphovascular invasion.
 - 3.4** T3 tumours can only be included if N0 both before and after neoadjuvant systemic therapy (cN0, pN0(sn), ypN0).

Exclusions

- 1.** Any pT0pN0-1 or pT1pN0 tumours after primary surgery.
- 2.** Any pT3pN1 or pT4 tumours. Initial stage cT3cN1 or pN1(sn) or cT4 in patients receiving neoadjuvant systemic therapy cannot be included, even if downstaging has occurred and the pathological ypT and N stage is lower.
- 3.** Patients who have 4 or more pathologically involved axillary nodes. For the purpose of this study protocol, nodal scarring after neoadjuvant systemic therapy will be considered as evidence of previous pathological nodal involvement and count towards the total number of involved axillary nodes.
- 4.** Past history or concurrent diagnosis of ductal carcinoma in situ (DCIS) of the contralateral breast, unless treated by mastectomy. Previous DCIS of the

ipsilateral breast if treated with radiotherapy (i.e. previous DCIS treated by conservation surgery not followed by radiotherapy would be considered eligible).

5. Bilateral breast cancer. However, patients who have undergone a prophylactic contralateral mastectomy can be included, if the breast was pathologically free of invasive tumour.

6. Previous or concurrent malignancy other than non melanomatous skin cancer and carcinoma in situ of the cervix. For previous DCIS see criterion 4.

7. Male.

8. Pregnancy, at the time of radiotherapy treatment.

9. Not fit for surgery, radiotherapy or adjuvant systemic therapy.

10. Unable or unwilling to give informed consent.

Randomisation

Randomisation to chest wall irradiation or no chest wall irradiation

Primary endpoint:

Overall survival

Secondary endpoints:

Chest wall recurrence

Regional recurrence

Disease free survival

Metastasis free survival

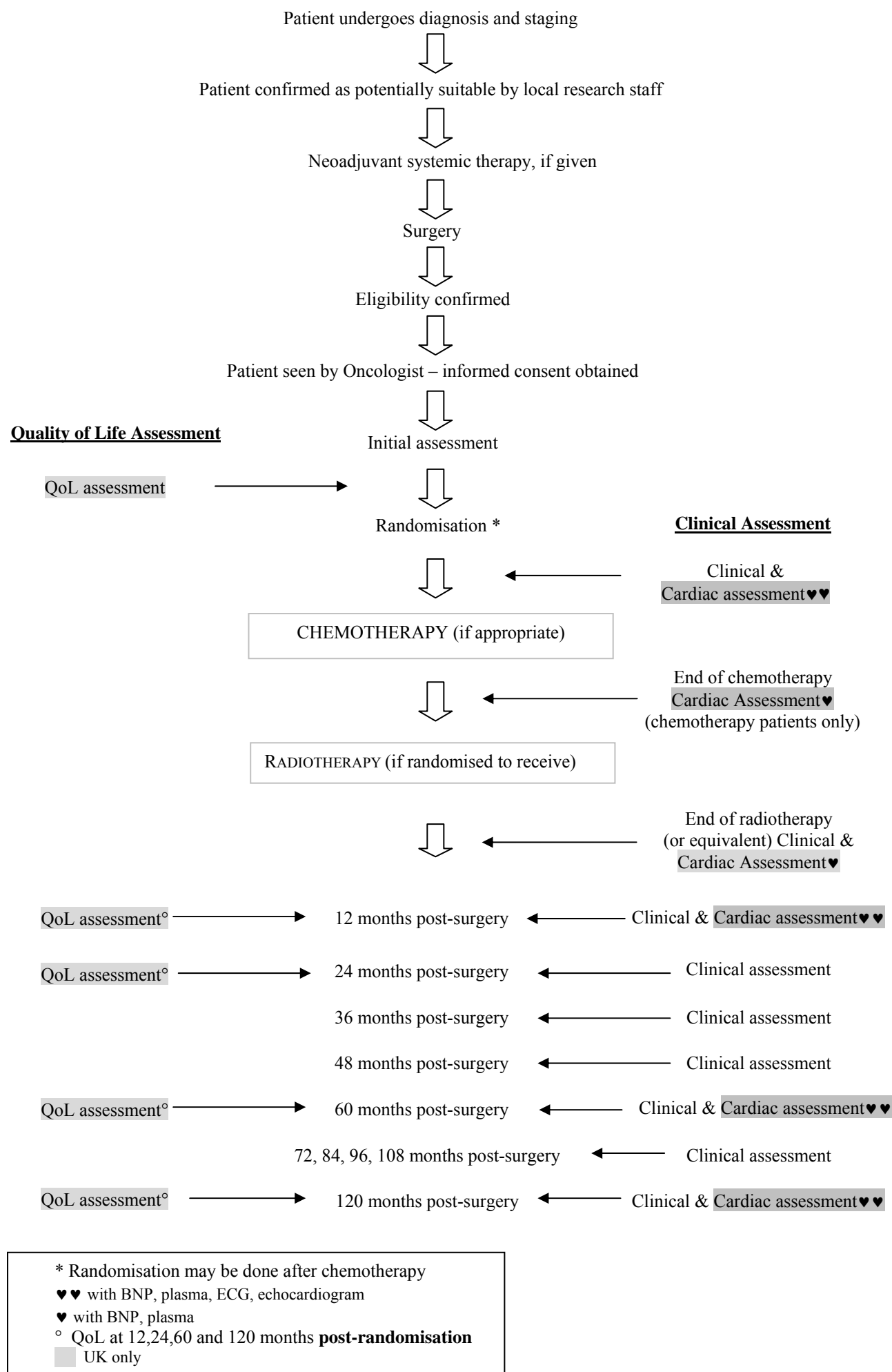
Cause of death (breast cancer, intercurrent disease [cardiovascular and non-cardiovascular])

Acute and late morbidity

Quality of life

Cost effectiveness

Follow up: 10 years



Visits(a)	Patients involved	Screening	Post (+/-) chemo pre (+/-) RT	Post (+/-) RT	1 yr	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr	8 yr	9 yr	10 yr	Recurrence ²
Investigations		Baseline 1	2	3	4	5	6	7	8	9	10	11	12	13	
Informed consent	All	X													
Medical history & examination (b)	All	X		X	X	X	X	X	X	X	X	X	X	X	X
Staging tests	All	X													
Contralateral mammography	All	X			A mammogram of the opposite breast, if appropriate, is recommended at least in alternate years for 10 years from the date of mastectomy										
Blood sampling	If consented to TRANS-SUPREMO	X													X
Tumour paraffin block from primary tumour ¹	All	X													
Tumour paraffin block at recurrence if available ²	All														X
Acute/ Late morbidity ³	All			X	X	X	X	X	X	X	X	X	X	X	
Cardiac symptoms and examination	If consented to cardiac sub study	X	X ⁴	X	X				X					X	X
Blood sampling for BNP	If consented to cardiac sub study	X	X ⁴	X	X				X					X	X
Electrocardiogram	If consented to cardiac sub study	X			X ⁵				X ⁵					X	X ⁵
Echocardiogram (c)	If consented to cardiac sub study	X			X ⁵				X ⁵					X	X ⁵
QOL and EQ5D economic assessment (d)	If consented to QOL sub study	X			X	X			X					X	

(a) Patients in the control arm MUST follow the same follow up schedule as irradiated patients.

(i) **The only exception are patients in the cardiac substudy who receive chemotherapy. This is the only group of patients who must attend a post chemotherapy visit.**

(ii) **For patients receiving chemotherapy, follow up will be on completion of radiotherapy or at 3 months after chemotherapy in non-irradiated patients.
For patients not receiving chemotherapy follow up will be on completion of radiotherapy or at 3 months after surgery in non-irradiated patients.**

(b) Questioning for symptoms of recurrent breast cancer, examination of loco-regional area and other relevant clinical areas for evidence of recurrence depending on clinical features.

(c) In centres where isotope ventriculography is the standard examination for patients requiring anthracycline containing chemotherapy, an echocardiogram will also be required at baseline. Echocardiography will be used for all subsequent time points in the study.

(d) Baseline (pre randomisation) quality of life assessment will be conducted in the clinic. All subsequent quality of life assessment questionnaires will be mailed to the patient.

¹ Tumour blocks required from all patients for purpose of audit. Tissue microarrays only constructed if patient consented to TRANS-SUPREMO.

² Recurrence defined as local and/or distant relapse and/or development of a contralateral breast primary. Blood and tissue samples should be obtained prior to any subsequent treatment commencing.

³ Morbidity will be measured using the RTOG/EORTC Radiation morbidity scoring system in all patients regardless of whether they are allocated radiotherapy or not. Any toxicity assessed as a Grade 4 or 5 Acute or Late Morbidity Score must be reported on a SAE/SUSAR report form.

⁴ For patients in the cardiac substudy not receiving chemotherapy, the post chemo/pre RT visit will not be required.

⁵ Echocardiogram and ECG repeated if B type natriuretic peptide (BNP) exceeds threshold value or clinical features warrant it.

Membership of Steering and Data Monitoring Committees and Trial Management Group

Trial Steering Committee

Prof. Barry Hancock, Sheffield (Chair)

Prof. Ian Kunkler, Edinburgh (Chief Investigator)

Dr. Niall Anderson, Edinburgh

Prof. John Bartlett, Edinburgh

Dr. Peter Canney, Glasgow (Co-Chief Investigator)

Dr. Irene Devine, ISD, Edinburgh

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Ms. Alison Walker, Edinburgh (Patient Representative)

Data Monitoring and Ethical Committee

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Dr. Paul Symonds, Leicester

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Prof. John Cairns, London

Dr. Peter Canney, Glasgow (Co-Chief Investigator)

Dr. Irene Devine, ISD, Edinburgh

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Prof. Galina Velikova, Leeds

Ms. Alison Walker, Edinburgh (Patient Representative)

1. INTRODUCTION

International consensus supports the routine use of adjuvant chest wall irradiation in women after mastectomy and systemic therapy for breast tumours ≥ 5 cm in diameter and with 4 or more histologically involved axillary nodes (Recht et al., 1998) or with a 20% 10 year risk of loco-regional recurrence (LRR) (Goldhirsch et al., 1998a). However the value of chest wall irradiation in women at intermediate risk of loco-regional recurrence with 1-3 involved nodes after mastectomy and a 10 year risk of loco-regional recurrence of less than 15% is uncertain. For such patients loco-regional radiotherapy is not standard care in most UK centres or internationally. Clinical trials of postmastectomy radiotherapy (PMRT) in this subgroup are an international priority (NIH consensus statement, 2000; Recht et al., 2001).

From a survey conducted amongst UK clinical oncologists there are wide variations in practice in the use of chest wall irradiation in women with 1-3 involved nodes after an axillary clearance (Kunkler et al., 2000). This may reflect the absence of definitive data from randomised trials assessing the value of adjuvant irradiation in this group of patients. A recent survey among European radiation oncologists of the use of PMRT in women with 1-3 positive nodes showed wide variations among those advocating PMRT from 19% in Italy to 74% in Spain and Portugal (Ceilley et al., 2005).

Of the 15 prospective randomised trials evaluating PMRT for axillary node positive patients receiving adjuvant systemic therapy, all but one show the ability of radiation to reduce LRR. The proportional reduction in risk of LRR remains fairly constant, between one half and two thirds. However, the absolute benefits range widely, from 6% to 21% (Fowble, 1999). The absolute reduction in risk ranged from 10% to 28% for patients with four or more nodes involved and from 3% to 23% for patients with 1-3 involved nodes. For T3 tumours, it ranged even more widely, from 10% to 45%. Whelan et al., (2000) in an overview have estimated the impact of loco-regional radiotherapy in current practice from all peer-reviewed published trials (median follow up at least 5 years) among patients receiving adjuvant chemotherapy or tamoxifen (or both) randomised to receive or not to receive radiotherapy. Radiotherapy was associated with a 75% reduction in odds of loco-regional failure, a 31% reduction in odds of tumour recurrence and 17% reduction in the odds of death. The effects of radiotherapy in terms of reducing recurrence and improving survival are similar in size to those of systemic therapy (EBCTCG, 1998).

Loco-regional failure after mastectomy and systemic therapy alone is commonest on the chest wall and considerably less common in the axilla or supraclavicular fossa. Very rarely it occurs in the internal mammary nodes. Most of the survival benefit is thought (but not proven) to be derived from chest wall irradiation.

The Oxford overview (EBCTCG, 2000) suggests that PMRT reduces breast cancer mortality in women with a 20% 10 year risk of loco-regional recurrence by 5%. Clinically significant gains in survival might also occur in women with a lower than 20% risk of local recurrence, for example those with 1-3 positive nodes treated by mastectomy, axillary clearance, systemic therapy and chest wall irradiation.

Randomised trials comparing mastectomy and systemic therapy with or without loco-regional irradiation have shown a 9-10% survival benefit at 10 years from the addition of loco-regional irradiation to adjuvant cyclophosphamide, methotrexate and 5 fluorouracil (CMF) in 'high risk' premenopausal women (Overgaard et al., 1997; Ragaz et al., 1997). A similar survival benefit has been shown in postmenopausal women at high risk of local recurrence (Overgaard et al., 1999). The larger trial from Denmark of 1061 premenopausal high risk patients with 1-3 involved nodes shows an 8% gain in

overall survival (62% vs 54%) from the addition of comprehensive loco-regional irradiation to systemic therapy. For the 1885 patients with 1-3 involved nodes from a combined analysis of the premenopausal and postmenopausal patients in the Danish Trials (Overgaard et al., 2007) overall survival at 14 years was 10% higher with the addition of PMRT (50% vs 40%, $p = 0.0001$). While survival benefit was shown in all subgroups of patients, the major benefit accrued to those with 1-3 positive nodes and in patients with tumours 5cm or less. The survival advantage of the addition of radiotherapy to CMF was greater (9%) in small (<21mm) and intermediate size (21-50mm) tumours, compared to 7% in larger tumours (>50mm). There were similar findings in the Danish trial of postmenopausal patients (Overgaard et al., 1999).

It is possible therefore that while loco-regional radiotherapy may confer most benefit in loco-regional control in larger tumours, a greater survival benefit might be conferred in smaller tumours and fewer numbers of involved nodes due to a lower competing risk of distant metastases (Harris et al., 1999). This hypothesis is supported by a recent retrospective analysis of three European Organisation for Research and Treatment of Cancer (EORTC) adjuvant breast cancer trials (van der Hage et al., 2003). It shows that patients with 1-3 positive nodes gained most in terms of survival (RR 0.48, 99% CI 0.31-0.75, $p < 0.001$). These data should be interpreted with caution since the analysis is retrospective. Long term (20 year) follow up of the Canadian trial of PMRT (Ragaz et al., 2005) shows a 7% gain in overall survival (57% vs 50%) from the addition of locoregional RT to systemic therapy. However in an accompanying editorial Whelan & Levine (2005) comment that in the 1-3 node positive group treated by PMRT, we remain dependent on subgroup analysis and level I evidence is still needed on the benefits of PMRT in this subset of patients. In node negative patients the results of PMRT are conflicting. No survival advantage was found in this subgroup in the Danish randomised trials (Overgaard M, 2002) or in combined analysis of the EORTC trials (van der Hage et al., 2003). A recent retrospective study (Jagsi et al., 2005) of a population of 887 node negative patients who had undergone mastectomy without adjuvant irradiation, showed that size >2cm, margin <2mm, premenopausal status and lymphovascular invasion were independent prognostic factors for loco-regional recurrence (LRR). Ten year LRR was 10% with one risk factor, 17.9% with two risk factors and 40.6% with three risk factors. However, even for T3N0 (stage IIb) tumours, the local recurrence risk can be less than 10% at 15 years in patients treated with adjuvant systemic therapy (Taghian, 2006). Furthermore a retrospective comparison of patients treated in a centre in Brussels by postoperative radiotherapy after mastectomy showed a 2.5%-6.9% overall survival benefit compared to a similar population of patients from the US SEER database treated without postmastectomy radiotherapy (Voordeckers et al., 2003). The authors acknowledge the limitations of a retrospective comparison and commend a randomised trial of adjuvant radiotherapy in node negative postmastectomy patients.

Uncertainty remains on the generalisability of the results from the Danish and Canadian trials to clinical practice, however, due to specific features of radiotherapy techniques, treatment volumes, regimes of systemic therapy and extent of axillary surgery which differ from those adopted in many cancer centres. The Danish trials (Overgaard et al., 1997; Overgaard et al., 1999) involved comprehensive irradiation of the axillary, internal mammary and supraclavicular nodes and a combination of photons and electrons to treat the chest wall. Most UK centres do not irradiate the internal mammary nodes and use photons alone to treat the chest wall. The intensity of the adjuvant CMF regime in the Danish trial has been considered suboptimal (Goldhirsch et al., 1998b) and the extent of axillary dissection inadequate. Anthracycline containing regimes of adjuvant chemotherapy have proved more effective than adjuvant CMF. They have largely replaced CMF for intermediate risk

breast cancer. There are few data on the interaction of anthracycline based adjuvant chemotherapy and PMRT in this group of patients.

The mean number of nodes removed was only seven, probably accounting for the high loco-regional recurrence rate (30%) observed in patients with 1-3 involved nodes, due to understaging. In the British Columbia trial too the loco-regional failure rate (10 year actuarial rate 16% and 15 year actuarial 33%) was higher than in other series with at least 5 years follow up with 1-3 positive nodes (6%-13%) reported by other authors (Recht et al., 1999; Goldhirsch et al., 1988; Kaufmann et al., 1993). A recent subgroup analysis of the Danish data, including only patients with 8 or more axillary lymph nodes removed, has however shown a 9% absolute survival benefit at 15 years, and a local recurrence risk reduction from 27% to 4% at 15 years (Overgaard et al., 2007). Furthermore, the patients with the best prognosis and the lowest local recurrence risk (11%) without radiotherapy still showed a survival benefit of 11% at 15 years with radiotherapy, but for the patients with the poorest prognosis, there was no effect on survival, despite a reduction in locoregional recurrence with radiotherapy (Kyndi et al., 2009). However, the loco-regional recurrence rate at 27% is much higher than in many North American series, challenging the generalisability of this data to contemporary practice.

The recent guidance from the UK National Institute for Clinical Excellence (2009) encourages recruitment of patients with intermediate risk breast cancer after mastectomy into the SUPREMO trial.

How exactly loco-regional radiotherapy interacts with systemic therapy in contributing to survival is still not clear. Systemic therapy is thought mainly to eradicate systemic micrometastases more effectively than loco-regional disease (Fu, 1985). Loco-regional radiotherapy may be important in preventing secondary dissemination from the residual loco-regional disease and might increase the potential for cure (Arriagada et al., 1995; Ragaz et al., 1997).

Data on the risk of loco-regional recurrence (LRR) in different patient subgroups are limited and conflicting (Recht, 1999). Recht et al. (1999) showed that from the ECOG trial data on 2,016 assessable patients that with a median follow up of 12.1 years for disease free survivors, the cumulative 10 year incidence of LRR (including simultaneous distant recurrence) was 13% for patients with 1-3 positive nodes and 29% for those with four or more positive nodes. These figures are lower than the Danish and British Columbia premenopausal trials which showed respectively 30% and 33% LRR for 1-3 nodes and 42% and 46% LRR for four or more positive nodes.

The Scottish Intercollegiate Guidelines Network (SIGN) advocate that postmastectomy radiotherapy should be considered for all premenopausal women at high risk of local recurrence (SIGN, 1998). The SIGN guidelines indicate that risk is a summation of factors, including tumour size (>5 cm), grade, nodal status, lymphatic invasion and involvement of deep margins. It remains unclear, however, what degree of benefit is achieved for particular subgroups of patients at intermediate risk (e.g. those with less than four nodes involved, tumours <5 cm or negative nodes and grade 3 histology or lymphovascular invasion). Nor is it clear what weight should be assigned to other factors, such as tumour size, grade and lympho-vascular invasion.

Some authors have attempted to use combinations of prognostic factors, such as tumour size and number of involved nodes, to define subgroups with more specific risks of LRR than single factors alone. As Recht (1999) points out, information on such combinations is limited (Fowble et al., 1988; Sykes et al., 1989; Pisansky et al., 1993). Recht et al., (1999) in a multivariate analysis of the ECOG data showed tumour size, number of involved nodes and ER status to be predictive of risk of LRR but not

age or menopausal status. Other prognostic factors, such as vascular or lymphatic invasion (Recht, 1999; Katz et al., 2000, Voogd et al., 2001), tumour grade (O'Rourke et al., 1994) and extracapsular nodal extension (Katz et al., 2000) increase the risk of recurrence. There may therefore be patients who are axillary node negative with risk factors for local recurrence for whom PMRT might confer a survival advantage in addition to a reduction in risk of loco-regional recurrence.

Recently Taghian et al., (2004) have reported from 5758 node positive women enrolled in the NSABP B-15, B-16, B-22 and B-25 trials that the overall cumulative incidence of locoregional failure was 13.0% in women with 1-3 positive axillary nodes compared to 24.4% and 31.9% in women with 4-9 and ≥ 10 nodes after mastectomy and doxorubicin containing adjuvant therapy. In multivariate analysis, age, tumour size, premenopausal status, number of lymph nodes and number of lymph nodes dissected were significant risk factors for LRF as first event. However compared to institutional or population based series, there is a much higher representation of patients who are premenopausal and under the age of 50 in the combined NSABP series (Olivotto, Truong and Chua, 2004). These authors also highlight the fact that the NSABP trials were primarily designed to assess different chemotherapy regimes rather than assess the role of PMRT. This may limit the generalisability of such trial data to clinical practice. The value of PMRT in women with 1-3 positive nodes or node negative but with other risk factors depend on whether the benefits in loco-regional control and survival outweigh treatment related morbidity and mortality. Morbidity may have a significant impact on quality of life. Complications of chest wall irradiation include pneumonitis, cardiac damage and rib fractures.

While data on cardiac morbidity from the Danish premenopausal and postmenopausal trials of PMRT show no excess in morbidity or mortality from ischaemic heart disease in irradiated patients (Hojris et al., 1999); the cardiac volumes irradiated in these trials were minimised by use of electron field techniques used to treat the medial chest wall and internal mammary nodes. This technique is not common outside Denmark. Tangential fields are more commonly used in the UK to treat the chest wall and some of the cardiac volume may be irradiated in order to encompass the chest wall. Techniques for minimising dosage to the heart vary between centres, some using positioning techniques (Canney et al., 1999) and others partial cardiac blocking (Landau et al., 2001). The Oxford overview of trials of postoperative radiotherapy (EBCTCG 1995, EBCTCG 2000) shows that a reduction in breast cancer mortality from radiotherapy is partially offset by an increase in non breast cancer mortality which is mainly cardiovascular. It is estimated that if radiation induced cardiovascular morbidity could be eliminated an extra 2-4% 20 year survival from radiotherapy might be achieved (EBCTG 2000). The Oxford overview includes many older radiotherapy trials where dosage to the heart was higher using radiotherapy techniques which would now be considered outmoded (Harris et al., 1999). Modern techniques expose the heart to considerably lower doses compared to previous decades (Taylor et al., 2007; Taylor et al., 2009). Estimates of treatment morbidity, mortality and quality of life need to be based on contemporary and commonly used radiotherapy techniques.

Although the cardiac risks of radiotherapy may be less with current techniques, there is increasing use of potentially cardiotoxic anthracycline containing adjuvant chemotherapy regimes and thus additional risks of chemotherapy induced cardiac morbidity and mortality (Bristow et al., 1978, Shapiro et al., 1998, Guldner et al., 2006, Hoening et al., 2007). Furthermore, the use of targeted agents such as trastuzumab, can also cause cardiac morbidity (Tan-Chiu et al., 2005, Romond et al., 2005, Robert et al., 2006, Smith et al., 2007). The long-term cardiovascular effects of systemic therapy may therefore also influence the balance of benefits and risks of even modern PMRT.

Neoadjuvant chemotherapy (i.e. chemotherapy given prior to surgery) is being increasingly administered for operable (stage II) breast cancers, both within and outwith clinical trials. The rationale for this approach is the opportunity for chemotherapy response monitoring, and the increased rate of breast conservation. Trials have demonstrated an equivalent overall survival for patients treated with neoadjuvant chemotherapy and patients treated with the same chemotherapy post-operatively (Bear et al., 2006, Mauri et al., 2005, Mieog et al., 2007). The indications for adjuvant radiotherapy after mastectomy are based on the evidence from trials discussed in the previous sections, and rely on the pathological staging. Due to the down-staging that can occur with neoadjuvant chemotherapy, the traditional pathological criteria can no longer be reliably applied, with the result that the indication for adjuvant radiotherapy can be even more uncertain than after primary surgery. The series of retrospective studies from the MD Anderson Cancer Centre of patients treated with neoadjuvant chemotherapy indicate that both the initial clinical tumour stage and the postoperative pathological stage are independent predictors of the loco-regional recurrence risk, even if a pathological complete response is achieved. (Buchholz et al., 2008, Garg et al., 2004, Huang et al., 2004, McGuire et al., 2007). There are however no randomised trials investigating the optimal patient selection for post-operative radiotherapy to the chest wall and/ or lymph node regions. The inclusion of patients treated with neoadjuvant chemotherapy in a trial of post-mastectomy radiotherapy will help provide an evidence base on which treatment decisions for this patient group can be based on in the future (Buchholz et al., 2008).

In summary, a large randomised trial is needed investigating the impact on loco-regional control, survival, quality of life, morbidity and cost effectiveness of postoperative radiotherapy to the chest wall in women at intermediate risk of recurrence following mastectomy, receiving neoadjuvant or postoperative systemic therapy (if indicated) and axillary clearance.

2. OBJECTIVES

To determine the effect of:

Ipsilateral chest wall irradiation following mastectomy and axillary surgical staging for women with operable breast cancer at 'intermediate risk' of loco-regional recurrence.

On the **primary endpoint** of:

Overall survival

Secondary endpoints:

- Chest wall recurrence
- Regional recurrence
- Disease-free survival
- Metastasis-free survival
- Cause of death (Breast cancer, Intercurrent disease [cardiovascular and non-cardiovascular])
- Acute and late morbidity
- Quality of Life
- Cost effectiveness

3. PATIENT ELIGIBILITY (see Appendix IX for clarification of clinical staging (c), pathological staging (p) and pathological staging following neoadjuvant therapy (yp)).

1.1 Stage II histologically confirmed unilateral breast cancer following mastectomy including the following pTNM stages:

- **pT1N1M0**
- **pT2N1M0**
- **pT2N0M0 if grade III histology and/or lymphovascular invasion**
- **pT3N0M0.**

If the tumour area comprises multiple small adjacent foci of invasive carcinoma then overall maximum dimension is taken to determine the size for T staging (see section 7.2.2 for a more detailed explanation). Multifocal or multicentric tumours can be included (pT1m; pT2m; pT3m). The size of the largest tumour focus determines the T stage classification (see section 7.2.1).

1.2 Stage II histologically confirmed unilateral breast cancer following **neoadjuvant systemic therapy** and mastectomy, if the original clinical stage was cT1-2cN0-1M0 or cT1-2pN1(sn)M0 and with the following (**ypTNM**) stages after neoadjuvant systemic therapy:

- **ypT1pN1M0**
- **ypT2pN1M0**
- **ypT2pN0M0 if grade III histology and/or lymphovascular invasion**
- **ypT0pN0 or ypT1pN0 or ypT0pN1** (pathological complete remission, or near complete remission).
- **ypT2N0**, independent of grade or lymphovascular invasion, of the original stage was cT3N0.

Also:

- **ypT3N0M0**, if original clinical staging was cT1-3cN0 M0 or cT1-3pN0 (sn) M0.

1.3 Unilateral invasive breast cancer that conforms to the initial clinical staging of criterion 1, but has been down-staged by **neoadjuvant** systemic therapy to **ypT0pN0 or ypT1pN0 or ypT0pN1** (pathological complete remission, or near complete remission). If tumour stage **cT3 or ypT3**, then nodal status must be N0 both before and after neoadjuvant systemic therapy.

2. Undergone total mastectomy (with minimum of 1 mm clear margin of invasive cancer and DCIS) and axillary staging procedure.

3.1 If axillary node positive (1-3 positive nodes [including micrometastases >0.2mm-≤2mm]) then an axillary node clearance (minimum of 8 nodes removed) should have been performed. Isolated tumour cells do not count as micrometastases.

3.2 Axillary node negative status can be determined on the basis of either axillary clearance or axillary node sampling or sentinel node biopsy.

3.3 Sentinel nodes identified in the internal mammary chain are considered pN1b or pN1c if histologically proven. Patients can be included in the trial with microscopic metastasis in the internal mammary chain detected by sentinel node biopsy, if not more than 3 tumour positive nodes in axillary lymph nodes. If not biopsied, internal mammary chain sentinel nodes are considered tumour negative for staging.

3.4 Before neoadjuvant systemic therapy, axillary ultrasound is advised. Abnormal axillary nodes based on imaging (mammogram or ultrasound) should be sampled by guided needle sampling or core biopsy. Where axillary ultrasound is normal, negative axillary node status does not require histological confirmation before starting neoadjuvant systemic therapy. Positive, or negative, nodal status may also be determined by sentinel node biopsy before start of neoadjuvant therapy.

4. Fit for adjuvant or neoadjuvant chemotherapy (if indicated), adjuvant or neoadjuvant endocrine therapy (if indicated) and postoperative irradiation.

5. Written, informed consent.

Additional explanation for the inclusion criteria:

1. Patients undergoing immediate breast reconstruction are eligible for inclusion.
2. Patients who are carriers of known pathological mutations in BRCA1 or BRCA2 genes are eligible for inclusion.
3. Neoadjuvant systemic therapy:
 - 3.1 Patients who have undergone mastectomy after neoadjuvant systemic therapy are eligible for inclusion. For determination of tumour stage and nodal involvement, please see Section 7.3.
 - 3.2 Tumour grade, hormone receptor status and Her-2 receptor status (or HER gene amplification) should be determined on a core biopsy taken before the start of neoadjuvant systemic therapy. Lymphovascular invasion may be assessed on both the core biopsy and post treatment excision.
 - 3.3 T2 tumours that are cN0 and remain ypN0 after neoadjuvant systemic therapy can only be included if grade III histology and / or lymphovascular invasion.
 - 3.4 T3 tumours can only be included if N0 both before and after neoadjuvant systemic therapy (cN0, pN0(sn), ypN0).

Exclusion criteria

1. Any pT0pN0-1 or pT1pN0 tumours after primary surgery.
2. Any pT3pN1 or pT4 tumours. Initial stage cT3cN1 or pN1(sn) or cT4 in patients receiving neoadjuvant systemic therapy cannot be included, even if downstaging has occurred and the pathological ypT and N stage is lower.
3. Patients who have 4 or more pathologically involved axillary nodes. For the purpose of this study protocol, nodal scarring after neoadjuvant systemic therapy will be considered as evidence of previous pathological nodal involvement and count towards the total number of involved axillary nodes.
4. Past history or concurrent diagnosis of ductal carcinoma in situ (DCIS) of the contralateral breast, unless treated by mastectomy. Previous DCIS of the ipsilateral breast if treated with radiotherapy (i.e. previous DCIS treated by conservation surgery not followed by radiotherapy would be considered eligible).
5. Bilateral breast cancer. However, patients who have undergone a prophylactic contralateral mastectomy can be included, if the breast was pathologically free of invasive tumour.

6. Previous or concurrent malignancy other than non melanomatous skin cancer and carcinoma in situ of the cervix. For previous DCIS see criterion 4.

7. Male.

8. Pregnancy, at the time of radiotherapy treatment

9. Not fit for surgery, radiotherapy or adjuvant systemic therapy.

10. Unable or unwilling to give informed consent.

4. TRIAL DESIGN AND STATISTICAL CONSIDERATIONS

Randomised to chest wall irradiation versus no chest wall irradiation

4.1 Null hypothesis

There is no significant difference in overall survival in patients at 'intermediate risk' of loco-regional recurrence from operable breast cancer treated by mastectomy, axillary surgical staging and, if indicated, neoadjuvant and/or adjuvant systemic therapy with or without chest wall irradiation.

4.2 Sample size and power

If the 10 year survival difference between the non-irradiated and irradiated arms of SUPREMO was 7% (56% vs 63% respectively), the sample size to detect a 7% difference in overall survival at 10 years with 80% power at the 0.05 level of significance would be 1600 allowing a 5% increase for loss to follow up and rounding up. As recruitment will take place over several years and the anticipated survival rates will be subject to error, it is also helpful to express power in relation to the number of deaths in the study at the time of the primary analysis. The hypothesised survival rates correspond to a hazard ratio of 1.255, and for 80% power with this hazard ratio, the necessary number of events (deaths) is 609.

4.3 Statistical plan

All analyses will be based upon the principle of intention-to-treat, and two-tailed significance tests and confidence intervals will be used throughout. Analysis of the primary outcome variables will be based principally on the calculation of 95% confidence intervals for the hazard ratios, based on a Cox proportional hazards model. The timing of the first published report is planned to be based on a minimum of 2.5 years of follow up. This will be subject to modification by the Steering Committee on the advice of the Data Monitoring and Ethics Committee.

While the size of the trial limits the analysis of the relationship between systemic therapy and radiotherapy in relation to the endpoints for the trial, it is proposed to conduct an exploratory analysis of this relationship.

5. STAGING

Staging will be conducted according to local centre protocol. Staging policies for each centre should be communicated to the trials office in advance of trial entry and any

changes to staging procedures during the conduct of the trial. Full blood count, liver biochemistry and chest radiograph should be considered.

6. GUIDELINES ON SURGERY

6.1 *Mastectomy and axillary node clearance*

6.1.1 A total mastectomy (including skin sparing mastectomy) and a minimum of a level II axillary clearance should be carried out (a minimum of **8** nodes, from one or more surgical procedures, confirmed pathologically).

or

6.1.2 For axillary node negative patients, a total mastectomy and other axillary surgical procedures are permissible: either an axillary node sample with a minimum of 4 pathologically confirmed nodes

or

6.1.3 Sentinel node biopsy if conducted in a centre which has audited evidence of <10% failure to identify the sentinel node in at least 30 patients.

6.2 *Breast reconstruction*

Patients undergoing immediate breast reconstruction are eligible for the trial. Participating centres must state their policy on radiotherapy and immediate reconstruction in advance of the trial and notify any changes in policy during the trial to the trials office.

7. GUIDELINES ON PATHOLOGY

7.1 *General guidelines*

UICC staging (6th edition) should be used.

7.1.1 The size of the primary tumour should be measured.

7.1.2 All primary tumours should be graded according to the Nottingham modification of the Bloom & Richardson grading system as modified by Elston and Ellis (1991).

7.1.3 The adequacy of the excision margin should be measured. An adequate margin is any margin that is deep, anterior or radial. The margins are to be clear of either invasive or non-invasive disease, that is invasive disease or ductal carcinoma in situ (DCIS). It does not include the presence or absence of lymphatic/vascular invasion.

7.1.4 A minimum of 8 axillary nodes should be examined in an axillary clearance (this can be from one or more surgical procedures).

7.1.5 All submitted axillary nodes in an axillary node sample should be examined

7.1.6 A copy of the pathology report on the primary tumour and axillary node(s) should be sent to the trials office.

7.1.7 The original reported grade and lymphovascular status will be accepted for the purpose of the trial.

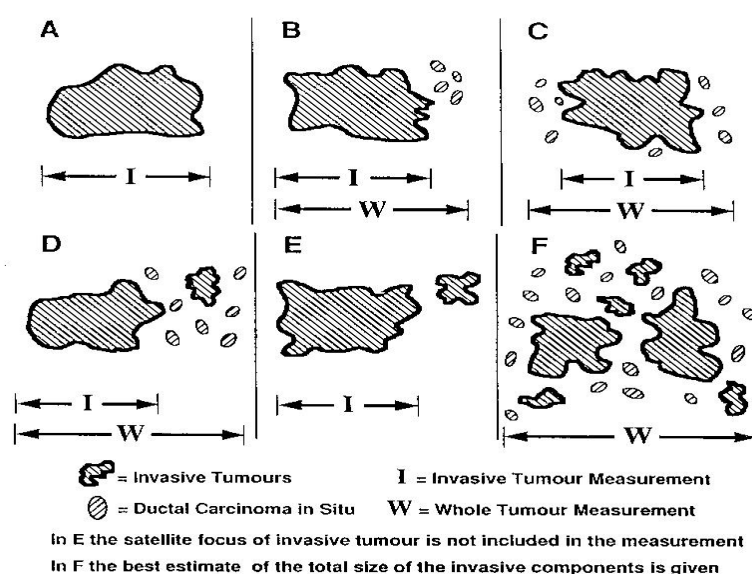
7.1.8 A password protected website for the trial will be provided giving examples of grading and lymphovascular invasion to facilitate standardisation of reporting between pathologists.

7.1.9 A panel of three pathologists will undertake the review of all cases entered by examining a representative H&E section taken from a tissue block submitted to the trial central laboratory. Each pathologist will review one third of the cases, randomly allocated, and assess grade and lymphatic/vascular invasion. The pathologists will be blinded to the original pathology report. Those cases where the review grade and lymphatic/vascular invasion status is in agreement with those originally reported will be reviewed no further. In those cases where there is disagreement between the reviewing pathologist and the original report there will be a formal review by all three reviewing pathologists to achieve consensus. Criteria for review will conform to current grading guidelines (Elston and Ellis, 1991).

7.2 Multifocal invasive cancer

7.2.1 If there is more than one discrete invasive cancer, the size of the largest focus of invasive cancer determines the T stage classification. This must be greater than 2cm for classification as a pT2 tumour and greater than 5cm for classification as a pT3 tumour.

7.2.2 If the tumour area comprises multiple small adjacent foci of invasive carcinoma then the overall maximum dimension should be taken and must be greater than 2 cm for classification as a pT2 tumour and greater than 5 cm for classification as a pT3 tumour (see Diagram F below):



7.3 Patients undergoing neoadjuvant systemic therapy

7.3.1 For determination of tumour stage and nodal involvement, the most advanced stage either clinically or pathologically is considered for the inclusion and exclusion

criteria. In the case of a pathological complete remission (inclusion criterion 1.3), then the clinical staging will apply, based on clinical and imaging examinations. This should comprise at least mammography and ultrasound of the breast and axilla. Results from other imaging modalities, if performed, such as MRI or FDG-PET may also be taken into consideration.

7.3.2 For this group of patients the core biopsy will be used to assess tumour grade and hormone status and Her-2 receptor status (or HER gene amplification). The Elston and Ellis modification of the Bloom & Richardson Grading System will be used as referred to in 7.1.2 above. Lymphovascular invasion may be assessed on both the core biopsy and the post treatment excision. A copy of the pathology report on the core biopsy should be sent to the trials office in addition to the reports detailed in 7.1.6.

7.3.3 For this group of patients nodal scarring is considered evidence of previous involvement to define the number of (originally) involved lymph nodes. For inclusion this should be 3 nodes or less.

8. GUIDELINES ON RADIOTHERAPY

General

Within each participating centre the radiotherapy technique should be standardised for all patients participating in the trial. This technique will be communicated to the radiotherapy quality assurance programme. Any change in technique must immediately be notified to the quality assurance programme.

8.1 Simulation and field irradiation

8.1.1 All patients should be simulated for the planning of chest wall irradiation.

8.1.2 CT planning to minimise dosage to the heart and lung is recommended. Where full CT planning is not available a simulator CT through the centre of the Planning Target Volume (PTV) is recommended. If this is not possible, an external contour with lung estimate is acceptable.

8.1.3 Treatment should be delivered using a technique that ensures an even dose distribution (within ICRU guidelines) using megavoltage photons and wedge filters or other appropriate method. Megavoltage electrons are permissible provided an adequate dose distribution is achieved.

8.1.4 Where it is not possible to treat the whole of the mastectomy scar within the tangential fields to limit dosage to lung and/or heart, the use of electron fields to treat the medial and/or lateral parts of the scar outside the tangential photon field should be considered. Care must be taken to avoid overlap of electron and photon fields.

8.1.5 Supraclavicular fossa and upper axilla

Where a level II axillary clearance has been performed and the axillary nodes are pathologically involved, a single direct anterior field covering the supraclavicular fossa and the apex of the axilla is recommended.

The anterior supraclavicular field may be angled 5-20 degrees to avoid the spinal cord. Shielding of the larynx may be used but should not shield the medial supraclavicular nodes.

8.1.6 Internal mammary chain

The CTV and PTV should preferably be indicated on the simulator images. As the internal mammary nodes are difficult to identify on CT, the PTV based on the internal mammary artery plus a 1.5 cm margin in lateral directions and 5mm in the dorsal direction should suffice in most cases.

8.2 Position of the patient

The patient will be treated in the supine position. Some form of immobilisation device is recommended such as an arm pole and/or vacuum bag. This position should be reproduced during simulation, acquisition of planning CT and during treatment.

8.3 Reproducibility of treatment position

The use of EPID (electronic portal imaging device) or equivalent is mandatory in centres where this technology is available. If electronic verification is not available it is strongly recommended that a port film is taken during the first week of treatment. Centres who are unable to verify patient position on set should contact the QA team to discuss options available to them.

8.4 Clinical target volume

8.4.1 The clinical target volume encompasses the skin flaps from 5mm below the skin surface and includes the soft tissues down to the deep fascia, but not including the underlying muscle and rib cage.

8.4.2 Reflecting international variations in radiotherapy practice and to maximise participation in the trial:

(a) UK centres, after a level II or III clearance, may elect to irradiate the Medial Supraclavicular Fossa (MSCF) and/or Internal Mammary Chain (IMC), if such is their centre's policy, in patients who have pathologically involved nodes and are randomised to chest wall irradiation. If they choose to do so they must notify the trial centre of their policy and technique prior to randomising patients in the trial.

(b) Non-UK centres after a level II or III clearance may elect to irradiate the Medial Supraclavicular Fossa (MSCF) and/or Internal Mammary Chain (IMC), if such is their centre's policy, in any patient in either arm of the trial. If they choose to do so, they must notify the trial centre of their policy and technique prior to randomising patients in the trial.

8.4.3 The lateral axilla, lateral to the Medial Supraclavicular Fossa (MSCF) and cranial to the tangential fields must not be irradiated. This is to avoid toxicity of combined surgical and radiotherapeutic treatment of this area, in particular the lymphovascular, venous and nervous structures. Since the lower axilla (part of level 1) is laterally adjacent to the breast, it is unavoidable to irradiate part of this in the tangential fields.

8.5 Planning target volume

8.5.1 The planning target volume encompasses the skin flaps. While the deep margin encompasses the deep fascia, the treatment volume inevitably includes the pectoralis major and rib cage. Depending on the energy used, build up may be necessary. To restrict the volume of lung and/or heart the surgical scar may have to be left out of the field medially and/or laterally.

8.5.2 The irradiated volume should extend medially to the midline, laterally to the mid axillary line and inferiorly to 1-2 cm below the level of the inframammary fold and superiorly to the level of the sternoclavicular joint. Care should be taken in setting the upper field margin to avoid irradiation of the axilla. If there is a clinical need to do so, it is acceptable to compromise PTV slightly taking into account location of the tumour and scar to spare organs at risk.

8.6 Treatment planning and reference point

8.6.1 Participating centres are encouraged to adopt 3-dimensional planning for trial patients as soon as it becomes available in their centre on Sim-CT or CT-Sim.

8.6.2 Dose inhomogeneity should not vary by more than 12% in the central slice. This should be between a point outside of lung and the maximum should be an isodose encompassing a 2cm square area (to allow for irregularities in calculation of maximum point dose by planning systems).

8.6.3 The lung density correction must be clearly stated when calculating the dose distribution. Centres should be aware of incorporating lung density correction on an individual plan.

8.6.4 Chest wall

Doses must be prescribed to the reference point which lies at or near the centre of the target volume (ICRU 50). This point is half way between the lung surface and the skin surface on the perpendicular bisector of the posterior beam edge. Maximum and minimum doses must also be stated to describe dose homogeneity and must follow ICRU 50 recommendations.

8.6.5 Supraclavicular fossa and upper axilla

The dose with photons should be prescribed to D_{max} (100% or a depth of 1.5cm using 6 MV photons; other energies may also be used).

8.6.6 The dose is prescribed to the ICRU 50 reference point for photons and to the 100% isodose for electrons.

8.6.7 Irradiation of large volumes of the heart and lung should be avoided by keeping the central lung distance to 3cm or less measured by computer tomography or simulator. Alternatively, verification of lung depth may be carried out using machine films.

8.6.8 Bolus may be applied to whole or part of the chest wall. Centres must specify their policy for the use of bolus in advance of participation in the trial and notify the trial administrator of any changes in policy during the trial. Centres should specify whether bolus is applied to part (e.g. the scar area) or all of the chest wall and for all

or a specified number of fractions and the thickness of bolus used for a given photon energy.

8.6.9 Centres electing to irradiate the internal mammary nodes must use CT planning for this purpose. The internal mammary nodes should be treated with a mixture of photons and electrons, using the electrons of appropriate energy and limited penetration to reduce the dose to the heart.

8.7 Sequencing of systemic therapy and radiotherapy

8.7.1 In patients not receiving chemotherapy, radiotherapy should be started within 12 weeks after the date of mastectomy. If more than one surgical procedure has been performed (e.g. the patient returns for an axillary node clearance), the date of final definitive surgery should be used. The date of final definitive surgery should also be used when patients have undergone a course of chemotherapy between initial and final surgery.

8.7.2 In patients receiving chemotherapy, radiotherapy should be started within 6 weeks of the end of chemotherapy.

8.7.3 All chemotherapy should be given before radiotherapy.

8.7.4 Trastuzumab, or other targeted biological agents, should be administered according to local policy.

8.7.5 Sequencing of endocrine therapy and chemotherapy may be according to local practice.

8.8 Dosage and fractionation

8.8.1 The dose distribution should be shown at least in the plane through the beam axes. The target area (planned target volume [PTV]) in this plane should be outlined.

8.8.2 Fractionation regimes

The recommended dose/fractionation regime is:

50 Gy TAD in 25 daily fractions over 5 weeks

Other admissible dose and fractionation schedules are:

45 Gy TAD in 20 daily fractions over 4 weeks

40 Gy TAD in 15 daily fractions over 3 weeks

42.4 or 42.56 Gy TAD in 16 daily fractions over 3 weeks plus 1 day

8.8.3 Breast reconstruction

Breast reconstruction is not a contra-indication to radiotherapy. Centres should state their radiotherapy dose and fractionation policy for patients undergoing radiotherapy after breast reconstruction in the trial. Cancer control should be the overriding concern.

8.9 Radiotherapy equipment

8.9.1 Megavoltage photons are recommended. Electrons of appropriate energy may be used. The choice of energy depends on the thickness of tissue between the skin surface and the underlying deep fascia.

8.9.2 Beam calibration should be carried out in accordance with a specified written protocol, preferably as described in the IPEM absorbed dose protocol (Code of Practice, 1990).

9. ACUTE AND LATE MORBIDITY

Baseline cardiac risk factors will be collected on all patients. Acute and late morbidity will be assessed using the EORTC/RTOG radiation morbidity scale [Cox et al., 1995](see Appendix VIII) **in all patients regardless of whether they are allocated radiotherapy or not.** Morbidity relating to all treatment modalities should be recorded. The acute morbidity will be assessed at the end of the course of radiotherapy or at 3 months post surgery for non-irradiated patients who have not received chemotherapy or at 3 months post chemotherapy for non-irradiated patients who have received chemotherapy. Late morbidity assessments will be carried out at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 months after surgery.

10. GUIDELINES ON ADJUVANT SYSTEMIC THERAPY

1. All patients should be considered for optimal adjuvant systemic therapy, if indicated.
2. For each patient, centres will be required to state whether (a) a taxane or anthracycline-containing regimen and (b) hormonal therapy has been used.
3. Choice of adjuvant systemic therapy should take account of tumour grade, lympho-vascular invasion, menopausal status, nodal status and oestrogen receptor status and if appropriate HER2 status.
4. In patients receiving adjuvant systemic therapy an anthracycline-containing regime for at least 3 months or 4 cycles should be encouraged.
5. The recommended minimum allowable starting dose per injection of doxorubicin in regimes such as adriamycin and cyclophosphamide (AC) should be 60mg/m² and in cyclophosphamide, adriamycin and 5-fluorouracil (CAF) or FAC is 50mg/m².
6. Where doxorubicin is given as a single agent in regimes such as Bonnadonna (4 cycles of adriamycin followed by 8 cycles of CMF) the recommended minimum starting dose per injection is 75mg/m².
7. The recommended allowable starting dose per injection of epirubicin in regimes such as Epirubicin and Cyclophosphamide (EC) is 90 mg/m² and in CEF or FEC is 50mg/m² when given on days 1 and 8 or 75mg/m² when given on day 1 every 21 days.
8. Where epirubicin is given as a single agent in regimes such as EpiCMF, the minimum allowable starting dose per injection is 90mg/m².

9. Taxane-containing regimes are permissible but it is recommended that they also incorporate anthracyclines. Centres will be asked to specify which regime they use.

10. It is recommended that all chemotherapy is given first and followed by radiotherapy in patients randomised to radiotherapy.

11. It is recommended that patients with oestrogen or progesterone receptor positive cancers should receive adjuvant endocrine therapy for a minimum of five years. For postmenopausal women tamoxifen or an aromatase inhibitor are advised. It is recommended that premenopausal women should receive tamoxifen, ovarian ablation or a combination or both. Centres will be asked to specify which endocrine therapy will be used.

12. It is acknowledged that there may be some patients, particularly the elderly or those with inadequate cardiac function or general medical condition, for whom a combination of classical or intravenous cyclophosphamide, methotrexate and 5 fluorouracil (CMF) may be more appropriate than an anthracycline-containing regime.

13. Patients can receive adjuvant trastuzumab or other targeted biological agents as appropriate, according to local practice.

11. REGISTRATION AND RANDOMISATION PROCEDURES

11.1 *Stratification will be by treating centre*

Centres should specify their policies of neoadjuvant and adjuvant systemic therapies and surgical procedures before entering patients into the trial.

11.2 *Randomisation procedure*

11.2.1 Consenting patients treated by neoadjuvant systemic therapy (if indicated), mastectomy, axillary surgical staging and adjuvant systemic therapy (if indicated) for intermediate risk breast cancer will be randomised in SUPREMO to receive or not receive postoperative chest wall irradiation.

11.2.2 Patients will be randomised by permuted blocks with the block length being varied randomly to minimise the effect of entry bias.

11.2.3 Randomisation should occur when radiotherapy is normally discussed. For centres participating in the Cardiac substudy (UK only), ideally patients would be randomised before the start of chemotherapy treatment. However it is recognised that the patient and/or clinician may wish to defer discussion about the main trial, TRANS-SUPREMO and the Quality of Life substudy until later during a planned course of chemotherapy. If discussion is deferred, the patient will be enrolled into the cardiac study with the proviso that they will consider randomisation to the main trial and substudies at a later point during their chemotherapy. If the patient declines randomisation at this later stage they will remain enrolled in the cardiac substudy, and follow the schedule outlined in section 20.

11.2.4 Eligibility and agreement to participate will be recorded on the Screening Log to be retained at each centre. Trial Screening Summary Forms should be completed and returned to the SUPREMO Trial Coordinator at ISD quarterly. Reasons for not entering patients in the randomised controlled trial will be recorded. After surgery eligibility will be confirmed. Patients who are interested will be given a patient

information sheet by the centre. Written informed consent to participation will be obtained.

11.2.5 For those patients consenting, the randomisation checklist should be completed by the centre and patients will be randomised through the Edinburgh trials office of the Information Services Division (ISD) Cancer Clinical Trials Team (formerly Scottish Cancer Therapy Network) in the UK and by agreement through other international trial organisations.

11.2.6 Once the patient has been formally entered into the trial, and the treatment allocation has been confirmed to the centre by fax, a letter should be sent to the patient's general practitioner (GP) on hospital-headed paper. Electronic notification to the GP is also acceptable where this is the local practice.

12. FOLLOW UP ARRANGEMENTS

12.1 Follow Up Clinic Visits

12.1.1 Follow up clinic visits will be made postoperatively for at least 10 years:

(a) - for patients in the cardiac substudy who receive chemotherapy, within 3 weeks of completing chemotherapy, before radiotherapy starts.

(b) i.- for all patients who have received chemotherapy, at the end of the course of radiotherapy or 3 months after chemotherapy in patients not receiving radiotherapy.

(b) ii. - for patients who have not received chemotherapy, at the end of the course of radiotherapy or 3 months after the date of mastectomy (or date of final definitive surgery, if applicable) in patients not receiving radiotherapy.

(c) - at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 months after date of mastectomy (or date of final definitive surgery, if applicable).

(d) - if the post radiotherapy visit or equivalent visit for non-irradiated patients falls within 6 weeks of the 12 month follow-up visit, then only 1 combined visit is required .

12.1.2 A 'Follow up' form will be completed at each visit. A ' morbidity' form will also be completed at these times. The acute morbidity form will be completed at the end of the course of radiotherapy only and the late morbidity form will be completed at 12, 24, 36, 48, 60, 72, 84, 96, 108, 120 months after surgery. For non-irradiated patients acute and late morbidity forms are completed at equivalent time points (see 12.1 b (i) and (ii). This is to avoid reporting bias.

12.1.3 An extra follow up visit will be required for patients participating in the cardiac substudy who receive chemotherapy (see 12.1.1a).

12.2 Recurrences

Any recurrences (local and/or distant relapse) and/or development of a contralateral breast primary) are to be documented on the Follow up form and details of treatment recorded on the Recurrence Form. **Blood and tissue samples should be obtained prior to any subsequent treatment commencing.** Causes of death will be sought from hospital or community medical records.

12.3 Mammograms

A mammogram of the opposite breast, if appropriate, is recommended at least in alternate years for 10 years from the date of mastectomy.

12.4 Serious Adverse Events (SAE's)

ICH GCP defines an SAE as any untoward medical occurrence shown in Box 1:

BOX 1

- Results in death
- Is life-threatening*
- Requires in-patient hospitalisation** or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in offspring of patient regardless of time to diagnosis).
- Is an important medical event (an event that jeopardizes the patient or may require intervention to prevent one of the other outcomes listed above).

* *The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.*

** *Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Hospitalisation for a pre-existing condition, including elective procedures, which has not worsened, does not constitute a serious adverse event.*

Other important medical events that may not result in death, are not life threatening, or do not require hospitalisation may be considered as serious adverse events when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in Box 1.

The SUPREMO trial uses standard radiotherapy schedules and unexpected serious adverse events are unlikely to occur. However all SAEs will be reported to the Data Monitoring and Ethical Committee. Expected adverse events from radiotherapy include skin reactions leading to chest wall tenderness and itching. Skin reactions are usually mild but are occasionally severe. Chest wall pain, usually mild and intermittent can occur. Rarely, osteoradionecrosis of the ribs can occur. Radiation pneumonitis can occur in 1% of patients if treated with tangential fields to the chest wall only. Cardiac damage may occur as a late effect.

SAEs should be reported if they occur during radiotherapy or within 30 days of the last radiotherapy session (fraction), whether or not they are related to the randomised treatment. They should also be reported if they occur at an equivalent time point in patients who are randomised to receive no radiotherapy.

In addition, any toxicity assessed as a Grade 4 or 5 Acute or Late Morbidity Score (see section 9) must be reported on a SAE/SUSAR report form. This applies for the entire follow-up period for the trial.

Patients who are consented and randomised before chemotherapy (eg. those recruited to the cardiac sub-study to obtain baseline bloods and cardiac assessments) may experience adverse events related to their chemotherapy. Any chemotherapy related SAEs that may, in the judgement of the responsible clinician, impact upon the delivery of the randomised treatment in SUPREMO should also be reported using the appropriate SAE/ SUSAR form. Table 1 lists the expected adverse events from chemotherapy which should and should not be reported as SAEs within the SUPREMO trial.

Table 1

Chemotherapy related SAEs that require reporting	Chemotherapy related SAEs that do not require reporting on SAE/ SUSAR form (unless they impact on delivery of the randomised treatment)
<ol style="list-style-type: none"> 1. Wound infections 2. Necrosis of the mastectomy skin flaps 3. Any cardiac event 4. Development of any other serious medical condition between date of consent and planned start of radiotherapy (or equivalent period for those patients randomised to not receive radiotherapy) 	<p>Hospitalisation due to:</p> <ol style="list-style-type: none"> 1. Neutropenia 2. Febrile neutropenia 3. Diarrhoea 4. Infections, including those to Hickman line, catheter. 5. Pyrexia 6. Sore throat 7. Nausea or vomiting 8. Cellulitis

13. ADMINISTRATION OF THE TRIAL

A senior trial coordinator will be appointed who will report to an executive committee responsible for the administration of the trial and to a committee of grant-holders for the trial. A trial coordinator will be appointed to assist the senior trial coordinator. The quality of life study will be supported by a trial coordinator.

14. DATA MONITORING

An independent Data Monitoring and Ethical Committee will be established and will meet every 6 months (or as often as they consider appropriate). None of the members of the committee will be involved in the trial. The committee will receive regular reports from the trial administration centre. It will submit its comments and recommendations to the Steering Committee and the Executive Committee.

Monitoring (source data verification) will be carried out by the Cancer Clinical Trials Team in Edinburgh on 10% of the patient data, and we have allowed for site visits in the UK. In addition we would expect to check 100% of patient consent forms in the UK. Higher levels of monitoring will be performed, if requested, by the Data Monitoring Committee, or if particular safety issues are identified by the investigators or the Trial Management group or Steering Committee.

15. ETHICAL APPROVAL

Ethical approval by a Multi-Centre Research Ethics Committee will be needed before the trial can be started. Participants will also need approval of their Local Research Ethics Committee (as appropriate until 1st April 2009). Approval by the National Cancer Research Network in the UK will be sought. The trial will be carried out according to guidelines of good clinical practice (ICH-GCP) as defined by paragraph 28 and Schedule 1 Part 2 of the Medicines for Human Use (Clinical Trials) Regulations, 2004, and the Clinical Trials Directive (2001/20/ECD) elsewhere in the European Union and follow the principles of research governance. Outside the European Union the trial will conform to international regulations appropriate to the local legal requirements.

16. PUBLICATIONS POLICY

A writing committee will be established by the grantholders which will be responsible for preparing publications of the trial for submission to peer reviewed journals. Similar writing committees will be established for TRANS SUPREMO, quality of life, cardiac, health economic and other substudies. The writing committee for the main trial will include a representative of the European Organisation for Research and Treatment of Cancer (EORTC) and other collaborating breast trial groups who have made significant contributions to the trial. Names of participating groups that have contributed to the trial will be clearly stated in publications reporting the results of the trial. Names of investigators who have contributed patients to the trial and their centres will be named as an appendix in articles submitted for publication. Articles reporting the results of the main trial and substudies will be circulated, where appropriate, by the writing committees to representatives of collaborating breast trials groups for comment prior to submission. An overview on the publications arising from the trial will be maintained by the Trial Steering Committee, who will be the arbiters in the event of any disagreement relating to publications.

17. RADIOTHERAPY QUALITY ASSURANCE PROGRAMME

The purpose of the radiotherapy quality assurance programme (RT QA)

The complex nature of modern radiotherapy carries inherent problems both in ensuring reproducibility and accuracy within a radiotherapy unit and, more particularly, when carried out on a multi-centre basis. Specific issues in the treatment of the chest wall, with or without lymph node pathways arise from the geometry of the treatment volume which varies in contour in all three planes with important radiation sensitive structures underlying the chest wall including the lung and myocardium.

Careful localisation, computerised planning, accurate verification of beam position and meticulous attention to alignment and matching during treatment are essential.

A quality assurance programme is “a mandatory prerequisite when aiming at high dose, high precision radiotherapy” (Horiot et al., 1993) and is an integral component of any radiotherapy trial as defined by the EORTC guidelines for trial protocols in radiotherapy (Bolla et al., 1995).

In this multi-centre randomised trial the quality assurance programme (QA) will enable confirmation that technical guidelines within the protocol have been understood and

implemented correctly by participants and that the dose prescription is delivered according to protocol with appropriate documentation.

This will ensure that clinical observations in terms of tumour control and normal tissue damage reflect differences in the randomised schedules rather than departures from trial protocol. Techniques used will be documented. This data will be available should differences in observed end points emerge.

In this way the definition of quality assurance as “all those planned and systematic actions necessary to provide adequate confidence that a product will satisfy given requirements of quality” (Standing Subcommittee on Cancer of the Standing Medical Advisory Committee: Quality Assurance in Radiotherapy, 1991) can be satisfied and the scientific worth of the parent trial be validated.

Background to the radiotherapy quality assurance programme

The QA programme will build on that developed for the START trial, which has provided a basis for consensus among radiotherapy centres in the UK.

All radiotherapy treatment relies on accurate reproducibility of the beams set up from day to day. This ultimately requires the use of light beams and laser alignments on skin marks on the patient. Inevitable variation occurs from day to day in a fractionated course of treatment which, even in the most rigorous setting, will result in field movements of several millimetres when daily verification films are taken (Westbrook et al., 1991).

Clinical sequelae may therefore arise because of imperfect technique. Inhomogeneity across the chest wall target volume may result in excess normal tissue damage to skin, subcutaneous tissues and ribs, and myocardial damage may result from the treatment of left sided tumours using techniques, which deliver significant doses to the heart. This may well result in an excess mortality from treatment (Cuzick et al., 1987) which can be reduced with careful attention to treatment technique (Fuller et al., 1991). The use of high doses to the nodal areas through a single anterior field will result in areas of the volume receiving greater than the prescribed tumour dose in larger fractions per day, or, in contrast, underdosage to the deeper parts of the volume if the tumour dose is prescribed to the anterior part of the volume only.

The hazards of shoulder stiffness, rib necrosis and skin fibrosis have been highlighted, but of equal concern is the question of tumour recurrence if inadequate treatment is given. These factors emphasise the importance of meticulous treatment technique in the proposed trial and the need for external quality assurance to avoid major clinical problems and to ensure equivalence of techniques.

Plan of the RT QA programme

The quality assurance programme will, having established precise details of radiation technique in each centre, focus upon measures by the QA team to the centres to verify adherence to treatment protocol and technique.

This follows the guidelines set out by the EORTC (Bolla et al., 1995) and will be co-ordinated by an experienced QA team based at Mount Vernon Hospital (Aird et al., 1995; Venables et al., 2001a; Venables et al., 2001b). It is based on an anticipated accrual to around 40 UK centres over a four year period. The programme will proceed as follows:

1. An initial questionnaire establishing precise details of technique to be used within the centre, together with specimen patient outlines or CT data, when available, to be used for ideal plans to be produced.

- * Target volume and treatment technique used together with methods of beam matching where appropriate.

- * Planning of radiation distributions across the treatment volume for homogeneity and prescription points.

- * Routine QC performed by the centre will be assessed and compared with current Institute of Physics and Engineering in Medicine (IPEM) guidelines.

2. A visit by the quality assurance team may be required prior to a centre entering the study to validate dosimetry in those centres which have not had dosimetry in a breast or chest wall phantom independently verified for the equipment currently being used. The QA programme for START revealed differences of nearly 10% in the delivered dose at the centre of a chest wall phantom (range 0.946-1.036) (8) and the range of delivered dose in patients will be larger than this due to variations in individual patient chest wall density and set up.

Measurements in phantoms allow the range of doses delivered during radiotherapy to be assessed.

3. The plans for the first 5 patients in the radiotherapy arm, from each radiotherapy treatment centre, together with verification images will be collected by the QA team.

4. Subsequently, 1 in 10 plans will be collected by the QA team to ensure continued protocol adherence.

5. In vivo dosimetry will be undertaken, preferably within the 1st week of treatment, in a subset of patients within the trial who will have thermo luminescent dosimetry (TLD) sent from the QA team. These patients will be identified at randomisation. It is anticipated that approximately 1 in 10 patients will have TLD sent from the QA team. Only UK patients will be selected for the in vivo dosimetry.

6. For all patients entered into the cardiac sub-study, copies of radiation port films, electronic portal images or CT plans should be sent for centralised documentation of the amount of heart within the irradiated fields. An electronic medium is preferred. If a participating centre does use film, each patient's film should be scanned preferably into DICOM format. The same is true for the treatment plan. The latter should be sent electronically (preferably batched on a CD).

Quality control of individual patients by department

The verification method must be independent of the planning system.

Analysis of QA programme

The data from the quality assurance programme will be analysed separately from the main trial. Major discrepancies from trial protocol will be notified to participating centres.

These will include:

1. Discrepancies in documentation, dose prescription and dose recording.

2. Dose inhomogeneity of more than 12% across chest wall treatment volume (-5% to +7%).
3. Hot spots (>100%) at field matchlines.
4. Inclusion of >3cm of lung in treatment volume.
5. Systematic errors of technique in any stage of treatment from planning through to implementation.

More detailed analysis of the quality assurance data will enable:

1. An independent review of variations in chest wall radiotherapy practice in participating centres.
2. Quantification of dose uniformity during the treatment period.
3. Correlation of physical parameters of radiation with trial end points:
 - (a) The association between dose variation across the treatment volume and tumour control.
 - (b) Variations in dose homogeneity and association with rib pain, fracture and necrosis.

18. BIOLOGICAL SUBSTUDY (TRANS-SUPREMO; UK, Ireland and EORTC only)

Biological Substudy

Background

The SUPREMO trial gives us a unique opportunity to expand our knowledge of the molecular mechanisms underlying the relapse of breast cancer and resistance to radiation therapy.

Radiotherapy is currently delivered to almost all women with early breast cancer undergoing conservation treatment, and to those with mastectomy at high risk of local relapse. Without irradiation, 20-40% of women will relapse locally over the succeeding 10-15 years (Cutuli, 2000).

Standard prognostic factors such as tumour size and grade, node status, age, ER status, absence of positive margins, extent of ductal carcinoma-in-situ and vascular invasion, do not define the 60-80% of patients in whom radiotherapy might be safely omitted (Fourquet et al., 2002). Factors mooted as potentially related to local relapse include reduced expression of bcl-2 (Silvestrini et al., 1997), over-expression of the IGF-1 receptor (Turner et al., 1997), expression of VEGF (Linderholm et al., 1999), cathepsin D (Ardavanis, et al., 1998), p53 (Zellars et al., 2000; Haffty, 2002), plasminogen activator inhibitor 1 (Cufer et al., 2002) and c-erb-B2 (Haffty, 2002; Koukourakis et al., 2003). Other proteins affecting local invasive potential, such as integrins and proteases, and proliferation, such as downstream activities in the Akt and MAP kinase pathways may also be important. One recent study has suggested that an activated wound signature may predict a poor outcome (Nuyten et al., 2004).

Increased risk of local relapse without but not with radiotherapy has been reported in association with positive immunohistochemical staining for p53, increased levels of GST and reduced expression of bcl-2 (Silvestrini et al., 1997). This suggests these factors may identify a group who benefit from radiotherapy. The role of BRCA1, BRCA2 and ATM is unclear in sporadic breast cancer, while cyclin D over-expression might contribute to radioresistance (Xia & Powell, 2002). There are no studies relating radiation response to other DNA repair proteins or factors involved in apoptosis, although several have been suggested to have a role in the development of breast cancer. Other factors involved in both these areas (for example Ku, PARP1, XRCC 1 and 3, Rad51, members of the bcl-2 family and caspases) are likely to have a role in radioresistance.

A recent study has used mRNA microarray expression profiling to identify young patients with node-negative early breast cancer at low and high risk of systemic relapse (van't Veer et al., 2002; van de Vijver et al., 2002). In this technique, mRNA levels were quantified using gene chip technology, and prognostic groups defined by patterns of expression of the subset of 70 genes showing a significant variation (2-fold or greater) between tumours. We hypothesise that a unique signature may be present for both local relapse and radiosensitivity. The aim of the present study is to identify these signatures and validate methods by which such patients can be identified in the clinic using the SUPREMO trial as a test system. The TRANS-SUPREMO study will allow the evaluation of potential pathways predictive of local relapse and radiosensitivity/resistance in the context of SUPREMO by constructing tissue microarrays from all patients enrolled in this trial. This approach should allow us to identify key molecular pathways for the future identification of patients most likely to benefit from radiotherapy. A similar approach is being used in early breast cancer,

where the use of standard prognostic factors to determine who should have adjuvant chemotherapy is being compared with decision making based on molecular signatures in the MINDACT trial.

In TRANS-SUPREMO we will construct tissue microarrays from paraffin blocks from mastectomy specimens from all patients randomised in the study. Some, but not most, centres involved in SUPREMO are routinely collecting frozen material from tumours. However the delay of 1-2 weeks between mastectomy and obtaining informed consent will preclude collection and storage of fresh or frozen material in the majority of centres. We will also collect whole blood, serum and plasma at randomisation, recurrence (local and/or distant relapse) and/or development of a contralateral breast primary to look for pharmacogenetic and protein markers of relapse/outcome. Further tissue will be collected, where possible, at recurrence (local and/or distant relapse) and /or development of a contralateral breast primary. For patients who undergo neoadjuvant systemic therapy, tissue from the core taken at diagnosis will also be collected, where possible.

Even in a study as large as the proposed SUPREMO study, the relatively small number of informative specimens (i.e. those from patients with relapsed disease) means that only a small number of individual factors can be tested in proteomic studies. Accordingly, we plan a strategy where we will look at the pattern of expression of a profile of plausible biologically-linked factors from defined pathways suggested as potential predictors by the profiling data, and further factors identified from the literature available at the time the proteomics analysis is carried out, as likely to influence local relapse or radioresistance. No systematic review has yet been carried out in either area to identify potentially important predictive factors. However, as discussed above we would anticipate that proteins involved in signal transduction, cell adhesion and invasiveness, and apoptotic pathways, would be prognostic for relapse, and that radioresistance would also be affected by DNA repair and cell cycle control pathways. Given that approximately 300 5micron sections can be cut on every TMA block, we anticipate that up to 100 factors could be tested. Carbone and coworkers, using matrix-assisted laser desorption-ionisation time of flight (MALDI-TOF) mass spectroscopy were able to define two prognostic groups of patients with resected non-small cell lung cancer exhibiting a four-fold difference in median survival using 15 mass spectroscopy peaks (Yanagisawa et al., 2003), suggesting that such a hypothesis-driven strategy has a good chance of discovering such profiles of relapse and radioresistance in patients with early breast cancer.

Having identified molecular signatures of risk of relapse and radioresistance, we will investigate this further in the much larger group of women receiving conservation therapy, where identifying those who do not benefit from radiotherapy would have major health service resource implications.

Aims

To identify molecular factors associated with increased risk of local relapse.

To identify molecular factors contributing to increased radioresistance.

Methods

(a) Molecular analysis by tissue microarrays

Tissue micro arrays (TMA) represent a significant step forward in our ability to perform translational research focusing on specific molecular pathways and developing multi-

factorial models of prognosis, rather than simplistic screening for single candidate genes.

For each patient a representative tumour-containing fixed tissue block will be requested from the appropriate pathology laboratory. Given the amount of tissue required for these studies it is not foreseen that removal of tissue will compromise the future diagnostic evaluation of patient samples. In cases where the block sent is the only sample available from the patient, consultation with the consultant pathologist of record will be undertaken to ensure that sufficient material remains to allow future diagnostic procedures to be performed. In the rare event that there is concern that removal of cores may compromise future diagnostic testing on the patients' tumour the patient will be excluded from the pathological study. The tissue will be sent by post to the central reference (banking) laboratory. On receipt each tissue block will receive a unique study identification code. Tissue from individual tumours will be stored in tissue arrays and also as standard tissue sections before the blocks are returned to the referring pathologist.

Briefly, a section of tissue will be stained using haematoxylin & eosin (H&E) to identify areas of tumour. Three tumour areas will be selected and 6 x 0.6 mm² cores of tumour tissue will be removed in total from each block. Experience in the laboratory of the investigator who will hold this tissue bank (JB) has shown that MLSO are able to select these tumour areas with a high degree of accuracy without recourse to a pathologist for each section. These cores of tumour tissue will be transferred to multiple (6) recipient blocks (100-300 cores per block) to form tissue arrays. From each tissue array up to 300 5 µm sections will be taken for analysis of biomarkers.

(b) Biological Analysis of tissues

The aim of the biological studies associated with the SUPREMO trial is twofold: to define a molecular signature of risk of relapse and radioresistance in patients with operable breast cancer, and to begin to characterise the underlying molecular events which relate to tumour relapse and patient response or failure to respond to the therapies applied in the trial. The "signature" is likely to include proteins and genes active in the key pathways involved in relapse and radioresistance, but these themselves may not be the factors directly responsible for the outcomes, but rather upstream or downstream activities modified as a consequence of the specific events leading to relapse or radioresistance. The signature will be useful both for identifying prognostic models for further studies and indicating avenues for further investigation aimed at modifying the risk of relapse or radioresistance. Currently, as discussed above, we would hypothesise that the risk of relapse is related to growth factors, signal transduction, cell cycle control and cell adhesion and invasiveness, while radiation response will partially overlap this, but also involve DNA (especially double-strand break) repair pathways and resistance to apoptosis. However, the specific factors analysed will be driven by the results of the mRNA expression array analysis.

Tissue arrays and sections will be analysed using immunohistochemistry (IHC) and fluorescent *in situ* hybridisation (FISH), to determine protein expression and RNA expression/gene amplification/deletion respectively, using standard methodologies and commercially available reagents. The Recht meta-analysis (Recht et al., 1999) showed that ER staining was associated with increased risk of loco-regional recurrence and therefore there would be an opportunity to test this hypothesis prospectively within the context of the current trial.

We will identify a panel of antibodies to test in triplicate on the TMA sections from the pathways described. Image analysis tools may be used to score the sections. For

economies of scale, consistency of staining and reproducibility of scoring these investigations will be performed at the end of the trial when all the samples have been collected, but before the individual outcome data is available, thus blinding the scoring from biases related to knowledge of the clinical course of each patient.

Informed consent to these investigations will be obtained at the beginning of the study when patients are randomised to radiotherapy or no radiotherapy. Since trial patients will not be identified until they have had their mastectomy and axillary clearance, obtaining consent at an earlier stage is not feasible.

Although our major interest is in local recurrence, this data set will be available for investigation of other phenomena such as risk of distant relapse, second primary malignancy etc. by other workers.

(c) Statistical power of tissue microarrays

Currently there is no model on which to base power calculations for hierarchical analyses of protein expression using tissue microarrays, nor are there previous series where large panels of antibodies have been used to establish prognostic signatures in this fashion. However, extrapolating from expression profiling studies (Dettling and Buhlmann, 2002) and mass spectroscopy studies (Yanagasiwa et al., 2003), where sample sizes required to produce highly significant results have typically been of the order of 60-80 patients, suggests that the number of events we anticipate (115 and 40 respectively in the no radiotherapy and radiotherapy cohorts) will provide sufficient power for this analysis.

A low stringency test of the univariate prognostic significance of each factor investigated by antibody staining will be carried out via CART classification tree modelling. All factors selected by this method will be subjected to analysis with a logistic discrimination model to identify those factors which together give the highest level of significance in discriminating between high and low risk of relapse.

(d) Other biological material

Plasma/serum and whole blood (for tumour and patient DNA) will be obtained from patients at baseline, and at disease recurrence (local and/or distant relapse) and/or development of a contralateral breast primary and stored for future studies of predictive biochemical markers.

(e) Quality assurance

A pathology steering committee including international representation has been established for the purposes of quality assurance.

(f) Trial management

The TRANS-SUPREMO sub-study will be supervised by a Trial Management Group comprising Prof. Allan Price, University of Edinburgh (Radiation Oncologist); Prof. John Bartlett, University of Edinburgh (Biochemist); Dr. Niall Anderson, University of Edinburgh (Statistician); Prof. Ian Kunkler, University of Edinburgh (Chief Investigator Main Study); Dr. Irene Devine (Principal Trial Coordinator), ISD Cancer Clinical Trials Team. International representation will be provided by Dr. Nicola Russell, Amsterdam (Radiation Oncologist).

19. QUALITY OF LIFE SUBSTUDY (UK only)

Background

Multimodal breast cancer therapy improves survival but also contributes to physical, sexual and psychological sequelae. These have been extensively documented for the first year of treatment and follow up. There are also late effects of treatment, such as the normal tissue effects of radiotherapy, the effect on body image of mastectomy and on sexual functioning from chemotherapy. Therefore it is essential to tease out the contribution of specific therapies on key aspects of quality of life.

The SUPREMO Quality of Life (QoL) study is designed to provide designated secondary endpoints to the trial. We will assess the subjective impact of mastectomy and chemotherapy, with or without additional radiotherapy to the chest wall over a ten-year period. Using a standardised approach it will be possible to compare the impact of the different treatment arms and to inform the balance between local tumour control rates and adverse treatment effects in terms of QoL.

The contribution of mastectomy and chemotherapy to QoL outcomes has been well documented (Ganz et al., 1992, 1998; Hopwood et al., 2002) but the additional effect of radiotherapy in mastectomy patients is unknown. Several studies help to inform on likely effects. On the one hand, Wallace et al., (1993) found few effects of radiotherapy on QoL in a small study of conservatively treated patients. There was a significant increase in nausea, tiredness, sleep disturbance and skin irritation on completion of radiotherapy but with a minimal impact on daily lives. Anxiety and depression were not increased at 6 months but one in three women did not feel radiotherapy was worthwhile.

In a much more robust study, Berglund and colleagues (1991) assessed patients 2-10 years after treatment in a randomised comparison of adjuvant chemotherapy or postoperative radiotherapy. Differences between the treatments were generally small. Radiotherapy patients had significantly greater problems with decreased stamina, symptoms related to their scar and anxiety; chemotherapy patients had significantly more problems with smell aversion. Findings were against the hypothesis that chemotherapy would be associated with late consequences in the physical, mental and social domains compared to radiotherapy.

Stanton et al., (2001) emphasised the need to assess functional aspects of QoL in relation to specific treatments for breast cancer. In a study of conservatively treated patients receiving radiotherapy, the authors found that treatment related functional status, and in particular breast pain, had an important predictive effect on QoL, overriding treatment related cosmesis.

Breast pain was also a predictor of depression, significantly so for women 5 years or more post diagnosis, and for physical health status. Arm oedema had a similar effect on QoL (Krishnan et al., 2001). Therefore the effect of local treatment on functional status should be a primary QoL outcome in the SUPREMO trial.

Others (Ganz et al., 1998) have found that mental health was comparable with general population samples when assessed several years post-treatment.

Recently the short-term effects of adjuvant chemotherapy have been assessed in 2062 women entering the START trials. Chemotherapy had a significant effect on

global health, body image, sexual functioning and depression, when type of surgery, age and time since diagnosis were controlled for (Hopwood et al., 2002).

It seems likely that the additional effects of radiotherapy in the SUPREMO trial will be small but may be significant for fatigue, physical functioning and chest wall pain and appearance. The expected outcome with respect to mental health is unclear, but data from the above studies suggest that, in general, rates of depression and anxiety rates are not significantly increased. Therefore, large samples would be needed to search for a small effect.

Rationale for QoL measurement

The main priority guiding the QoL approach is to select measures that are standardised and scientifically robust so that the data obtained are valid and reliable. There is an important opportunity to use measures that have been selected for other national breast cancer trials that would allow comparison of results. This is increasingly important for the process of informed decision making for future patients, and to facilitate familiarity with QoL data for clinicians and nurses helping patients with these decisions.

The key effects of treatment and relapse on QoL are hypothesised to be on general symptoms such as fatigue, chest wall symptoms, appearance of the chest wall and psychological distress. Physical functioning, role and social functioning and specific adverse effects of treatment will also be recorded.

The QoL domains of importance will therefore include the following:

- * a core quality of life measure to detect general effects of treatments on QoL
- * a breast cancer module to reflect specific symptoms and effects relating to the effects of treatment
- * a body image scale to assess the impact of treatment on appearance and attractiveness following surgery, chemotherapy and radiotherapy
- * a measure of anxiety and depression that indicates clinical levels of distress

Therefore a preference for measures used in the ABC and START Trials emerged. There is sound knowledge of their performance and of analysis methods and interpretation of outcome data. Detailed manuals support the EORTC scales. Scoring procedures and reference data are available for the BIS and threshold scores for the HADS are widely available. Patients in the START trials with excellent compliance rates have supported this combination of scales. They do not appear to be burdensome to patients, providing care is taken to avoid those who are seriously ill.

Measures

1. Quality of life: the EORTC core quality of life instrument EORTC QLQ-C30 (Aaronson et al., 1993). This is a 30 item cancer questionnaire comprising five functional scales (physical, role, cognitive, emotional and social), global quality of life, three symptom scales (fatigue, pain, nausea and vomiting) and a number of single items.

2. Breast cancer specific module EORTC BR-23. This is a 23 item questionnaire designed to be used together with EORTC QLQ-C30. It comprises scales related to chemotherapy specific side effects, shoulder-arm problems, body image, sexuality and future perspective (Sprangers et al., 2001).

3. Body image: The Body Image Scale - BIS (Hopwood et al., 2001)

This is a 10-item scale designed specifically for use with cancer patients to assess aspects of attractiveness, sexual attractiveness and feelings or satisfaction with appearance. (4 items are included in the BR23 and will not be duplicated).

The BIS has very good psychometric properties and has been used in the ABC and START trials, as well as European breast cancer trials. A threshold score for a morbid level of body image concerns has not been derived but there is extensive reference data for subgroups of patients receiving mastectomy or conservative surgery, with or without chemotherapy or tamoxifen (Hopwood et al., 2001, Hopwood et al., 2002).

4. Psychological Distress: The Hospital Anxiety and Depression Scale – HADS (Zigmond & Snaith 1983)

The HADS is a 14-item scale (7 items for depression and 7 items for anxiety) designed to measure affective disorder in cancer patients. Threshold scores have been derived that enables the prevalence of clinical levels of anxiety or depression to be estimated. A comparison of instruments showed the HADS to be superior in measuring anxiety and depression when compared with a psychiatric interview (Ibbotson et al., 1994) and it is the most widely used self-report measure of psychological distress used with cancer patients.

5. Cost effectiveness will be assessed by calculating the incremental cost per life year gained and the incremental cost per additional quality-adjusted life-year (QALY). The EQ5D (EuroQol, <http://www.euroqol.org/>) will be used in order to quality-adjust survival (Brooks, 1996). This measure is widely used in economic evaluation and is readily collected using a self-completed questionnaire. It comprises five simple questions (mobility, self care, ability to undertake usual activities, pain/discomfort, and anxiety/depression) each with only three possible responses. The EQ5D will be given to patients in the quality of life study along with the other quality of life questionnaires. QALYs will be estimated using an established set of EQ5D values (Dolan, 1997).

6. An open-ended question, inviting comments from patients will be added at the end of the questionnaire booklet.

Endpoints

Primary QoL endpoints will be:

1. Fatigue (QLQ-C30)
2. Physical functioning subscale (EORTC QLQ-C30)
3. Chest wall, shoulder and arm symptoms (EORTC BR23)
4. Body image (BIS)
5. Anxiety and depression (HADS)

Descriptive data will be obtained for the following domains from the EORTC:

- Role functioning
- Social functioning

- Sexual functioning
- Pain, nausea and vomiting

It is hypothesised that the experimental arm will result in an increase in symptoms/decrease in function in the primary outcome domains (either singly or in combination) compared with the control arm. This will need to be considered against the benefit, if seen, in local disease control.

Breast Reconstruction

Breast reconstruction is not a specific QoL outcome parameter but we need to be able to provide descriptive data for these patients. Therefore date and type of reconstruction (immediate or delayed), autologous tissue graft (TRAM, DIEP or LD Flap) or implant reconstruction will be annotated in the clinical forms. The most important QoL aspect of reconstruction is body image: this will be adequately captured by the body image scale and data are available for comparison from other published work using the same scale (AL-Ghazal et al., 2000). Minimal additional QoL parameters for this group will be HADS anxiety and depression and the EORTC breast cancer module (BR23).

Plan of study

There will be a detailed multicentre study of the patients' quality of life after chemotherapy and after additional radiotherapy in the experimental arm. A subset of centres will take part in the QoL study and, in these centres QoL assessments will form an integral part of the trial for all consenting patients. Centres will choose whether or not to opt in to the QoL protocol but the geographic (and socio-economic) distribution of participating centres will be monitored to ensure that they are representative of the trial as a whole.

Selected hospitals will be asked to participate if an imbalance occurs. This method has been used successfully in the START Trial and no intervention by the Trials office was required.

The assessments will take the form of serial patient self-report questionnaires, using validated measures that have been used successfully in the ABC and START Trials. Baseline QoL compliance in the START Trial, involving over 2000 patients, was 98.5% and has remained high at 6 months follow up.

Eligibility

All patients from selected centres who:

- * are entered into the SUPREMO Trial
- * consent to take part in the QoL study
- * are willing and able to complete the questionnaires

Sample size and statistical considerations

Although guidelines have been suggested for the size of score changes that represent clinically significant differences in QoL scores for EORTC QLQ-C30 (Osoba et al., 1998; King, 1996), these vary for the subscales and further research is ongoing. For this trial, sample size was considered as an estimation problem rather than a problem of testing of significance.

With 200 evaluable patients per group the proportion of patients exhibiting a particular side effect or specified degree of morbidity on a QoL domain will be estimated with a standard error of 3.5% or less. The corresponding difference between the groups will be estimated with a standard error of 5% or less.

The standard error of the difference in the means for any continuous variable will be 0.1 standard deviations. In order that QoL may be monitored to this level of precision for five years after randomisation, the target for entry will be double the nominal figure (800 patients in total), which allows for attrition due to death or withdrawal of cooperation at a rate of 13% per year.

All reasonable efforts will be made to ensure full and correct completion of the self-report questionnaires. The QoL booklet will contain standardised instructions for completion. When individual items are missing, the following procedures, which have been used in other studies, will be adopted:

- * where the item missing is a single QoL item it will be recorded as missing
- * where the missing item forms part of a brief scale or subscale, a pro-rata procedure will be used depending on the total number of items in the subscale:

There are known age effects for psychological distress, body image, breast symptoms, sexual and physical functioning and these will be controlled for in the analysis.

Timing of assessments

Baseline:

After obtaining informed consent, the first assessment for all patients will be completed in the clinic prior to randomisation with explanation of the questionnaires by a member of staff.

Follow-up:

All follow-up questionnaires will be mailed from the Trials office, by the QoL study co-ordinator, to minimise staff burden and allow patients to complete the forms in their own time, away from the treatment setting. Subsequent follow up for QoL assessment will be at 1, 2, 5 and 10 years from randomisation as in the protocol.

Close links will be kept with the Breast team and patients' general practitioners to check that the patient is alive and fit to participate, prior to future mailings. This is important given the emphasis on long-term follow-up.

Patients experiencing a relapse

Patients who have experienced a relapse will be asked to continue to complete questionnaires, although it is appreciated that some will not do so. At each due assessment point patients will be asked to complete a quality of life assessment unless they do not wish to continue in the QoL protocol.

Statistical aspects

The principal statistical method used will be a repeated measures of analysis of covariance as this makes allowance for observations that are missing and through

providing overall tests of treatment by time interaction and the main treatment effect, avoids some of the problems arising from multiple testing.

Trial management

Staff: Quality of Life Study Co-ordinators: This part of the trial will run under the guidance of Professor Galina Velikova. The staff running the QoL study will be based at the Centre for Population Health Sciences, the University of Edinburgh. Close links will be maintained with the trials team at ISD, where the main trial database is held to ensure correct, up-to-date patient information is available to the QoL study for follow-up purposes.

In the hospitals: It is intended that each participating hospital will identify a person responsible for the conduct of the QoL trial. This person will explain the study to the patient and ensure that the patient knows how to complete the QoL questionnaire booklet, will check that it is completed correctly and that it is forwarded to the trials office.

Informed consent and ethical issues

Ethical approval for the QoL substudy will be obtained at the same time as submitting the main trial protocol. The local investigator is responsible for obtaining each patient's signed informed consent prior to the administration of the baseline questionnaire.

Patients with clinically significant scores on the HAD scale (combined score above 19) should be further assessed clinically. This will be explained in the Patient Information Sheet. Patients will be asked to consent to information about the HADS score being passed on to their general practitioner.

20. CARDIAC SUBSTUDY (UK only)

Background

Recent studies of radiation toxicity in the treatment of breast cancer show that the effects on normal tissues can constitute a significant clinical problem and particularly increased cardiac mortality may offset any potential survival benefit (Cuzick et al., 1994; Host et al., 1986; Rutqvist & Johansson 1990; Rutqvist et al., 1992; Trott 1991; Gagliardi et al., 1996; Haybittle et al., 1989). There are no data on non-fatal late cardiac damage, but it seems likely that non-fatal ischaemic heart disease and heart failure may also be induced. An excess of cardiac deaths starts to manifest itself at about 7 years post radiotherapy and increases year on year thereafter (Rutqvist et al., 1992). Thus, reported values are dependent on length of follow up.

The maximum heart distance is the distance from the posterior field border of the tangential fields to the most anterior border of the heart on the simulator film and correlates well with the volume of myocardium included in the target volume (Canney, unpublished data).

Hurkmans et al., (2000) used the relative seriality model to calculate the Normal Tissue Complication Probability (NTCP) for heart damage for increasing values of the maximal heart distance. If this parameter is less than 1.5cm the NTCP for cardiac toxicity was calculated to be < 1%. The dose used for this calculation was 50 Gy in 25 fractions. It is important to note that the value of 1.5cm may not apply for different doses, fraction sizes or patients receiving cardiotoxic systemic therapy.

There has been no recent long term prospective assessment of potential cardiac morbidity in patients having cardiotoxic treatments as adjuvant therapy for breast cancer. In particular combinations of cardiotoxic agents may introduce additional risks of late morbidity or mortality.

B type natriuretic peptide

B type Natriuretic Peptide (BNP) is synthesized in the myocardium and increased levels are found in serum in patients with left ventricular dysfunction. BNP has a high negative predictive value for the diagnosis of left ventricular systolic dysfunction (McDonagh et al., 1998).

The power to predict normal cardiac function by a low plasma value is further enhanced when combined with the standard 12 lead electrocardiogram (Vrtovec et al., 2003). These clinical investigations merit assessment in the setting of breast cancer therapy.

Primary aim

To assess the utility of B type natriuretic peptide in identifying and predicting cardiac toxicity in patients undergoing adjuvant radiotherapy and/or chemotherapy.

A subsidiary aim is to store blood for evaluation of potential future markers of cardiac function and, in addition, to look for pharmacogenetic and protein markers of relapse/outcome of breast cancer.

Schedule of investigations

Echocardiography, ECG and blood for B type Natriuretic Peptide plus cardiac history, clinical examination (height, weight, BP, pulse, clinical signs of heart failure) to be obtained:

1. **Before** radiotherapy or chemotherapy starts
2. At 1, 5 and 10 years post surgery and
3. At recurrence (local and/or distant relapse) and/or development of a contralateral breast primary. Cardiac assessments and blood for BNP should be taken prior to any subsequent treatment starting.

In addition, patients will have blood taken for BNP plus cardiac history, clinical examination (weight, BP, pulse, clinical signs of heart failure) at the following timepoints:

- Within 3 weeks of completing chemotherapy and before any radiotherapy starts (this visit applies only to patients who receive chemotherapy)
- On completion of radiotherapy, or at 3 months post chemotherapy in patients receiving chemotherapy but who do not undergo radiotherapy, or at 3 months post surgery in patients who do not undergo chemotherapy or radiotherapy.

Plan of investigation

Patients should be approached for consent to participate in the cardiac substudy either at the patient's first appointment to discuss chemotherapy or, if chemotherapy is not planned, when radiotherapy is discussed. Baseline cardiac investigations should be ordered and baseline bloods for BNP taken once consent to the cardiac sub-study is obtained. Consent to the main trial, TRANS-SUPREMO and the Quality of Life substudy should ideally be obtained at the same time. However it is recognised that the patient and/or clinician may wish to defer discussion about the main trial, TRANS-SUPREMO and the Quality of Life substudy until later during a planned course of chemotherapy, particularly where the patient is also being approached about participation in a chemotherapy trial. If discussion is deferred, consent may be taken for the cardiac substudy alone with the proviso that the patient agrees to be approached about the main trial, TRANS-SUPREMO and the Quality of Life substudy at a later point during chemotherapy. If, post chemotherapy, the patient declines randomisation to the main SUPREMO trial they will remain enrolled in the cardiac substudy and complete the schedule of investigations as outlined above.

Consenting patients will have a baseline history (including family history of coronary heart disease and personal history of cardiac disease and cardiac symptomatology), clinical examination, serum cholesterol, electrocardiogram and assessment of left ventricular function by echocardiography. For patients in centres where isotope ventriculography is the standard investigation for patients undergoing anthracycline containing chemotherapy, an echocardiogram will also be carried out at baseline. Echocardiography and not isotope ventriculography will be the follow up investigation at all subsequent time points outlined in the schedule of investigations. Data collection for the various time points of the cardiac substudy including blood pressure, cardiac symptoms of chest pain, breathlessness, ankle swelling and palpitations will be collected by a research nurse in each participating UK centre. A suitably qualified clinician must complete the 'Clinical Signs of Heart Failure' section.

All ECGs and a digital recording of the echocardiogram images will be sent to the trials office for analysis by a core laboratory. Blood from patients will be collected in chilled EDTA tubes and plasma separated by local biochemistry labs before storing at -80°C. A whole blood sample will be sent immediately in heparinised tubes to the central laboratory in Edinburgh for analysis of BNP within 72 hours. Centres will be notified of the result within 7 days with a copy also sent to the trials office. Results will be documented in the CRF and forwarded to the trials office. If BNP becomes elevated above the normal range (0-100pg/ml) during the study period, the patient will be recalled for clinical and cardiac assessment by the local investigator and referred, if necessary, to a cardiologist. The local investigator will request ECG and echocardiography in the participating centre to assess cardiac function. It is recommended that patients with new and increasing cardiac symptomatology or a raised BNP level are referred to a cardiologist for assessment. Copies of clinical correspondence, copies of ECGs and echocardiograms performed locally in relation to any such events will be sent to the trials office, including digital images of echocardiograms for analysis in the core echo-lab. Advice on the management of individual patients will be available from the Chief Investigator (Dr. Peter Canney) and the trial cardiologists (Dr. Martin Denvir, Dr. Theresa McDonagh and Dr. David Northridge).

It is recognized that radio-isotope ventriculography would be the most reproducible method to assess changes in left ventricular systolic function but lack of availability in all centres and expense preclude this.

In patients randomized to chest wall irradiation, the maximum heart distance at simulation will be measured on beam's eye view.

Statistical considerations

The cohort of patients used to assess the negative predictive value of BNP in this setting will therefore be a combination of patients randomised into the main SUPREMO trial and also those who agree to the cardiac substudy pre-chemotherapy but later decline the main randomisation. Assuming a 5% rate of cardiac dysfunction within the first year and an annual rate of 3% in years 2-10 then the number of patients needed to provide adequate precision in estimating NPV (negative predictive value) will be 300 (this assumes estimation of NPV of approximately 90% with a confidence interval of total width 8 percentage points, ie a 95% CI of (86,94)%).

21. HEALTH ECONOMIC SUBSTUDY (UK only)

Aim

The economic study will assess the cost effectiveness of adjuvant irradiation.

While the initial treatment costs for those receiving chest wall irradiation will be higher, if the irradiation is successful the better outcomes for patients might be expected to be associated with lower future resource use. Irradiation might use sufficiently few additional resources that when combined with the savings in future treatment costs that it is cost-reducing. However, it is more likely that the net effect of irradiation will be to increase costs overall. Thus it is anticipated that the focus of the economic evaluation will be on the incremental cost per quality-adjusted life-year (QALY) from irradiation.

Eligibility

All patients from selected UK centres who:

- are entered into the SUPREMO Trial
- consent to take part in the Health Economics study
- are willing and able to complete the patient diary

Sample size

Since it is difficult to estimate the underlying distribution of costs to calculate an appropriate sample size, it is proposed to cost the treatment received by all consenting UK trial participants and the future costs of those in either arm of the trial with suspected or actual recurrence or morbidity. The estimation of QALYs will be based on data gathered from the sub-sample taking part in the Quality of Life study.

A subset of UK centres will take part in the Health Economics study and are expected to be those sites who are also participating in the Quality of Life study.

The assessments will take the form of a single patient self-reporting diary to be given to consenting patients by a member of staff at the centre at the time of randomisation to the SUPREMO trial. There will be separate diaries given to patients dependent on whether the patient is randomised to receive radiotherapy to chest wall or randomised to receive no radiotherapy to chest wall and whether the patient received post-operative chemotherapy. These diaries are colour coded for clarification at sites to ensure that the correct diary is given to the patient based on their randomisation and whether the patient received post-operative chemotherapy.

For those patients randomised to receive radiotherapy to the chest wall and received post-operative chemotherapy, the Health Economics patient diary will collect details of any visits to a health professional that the patient made during the period between the end of their post-operative chemotherapy and the commencement of their course of radiotherapy, information on the patient's radiotherapy appointments and details of any visits to a health professional that the patient has made during their course of radiotherapy and during the period up to 8 weeks after the end of their radiotherapy.

For those patients randomised to receive radiotherapy to the chest wall and received surgery and hormonal therapy alone OR neoadjuvant systemic therapy and surgery +/- postoperative hormonal therapy, the patient diary will collect details of any visits to

a health professional that the patient made during the period between the date of their last definitive surgery (mastectomy or axillary clearance) and the commencement of their course of radiotherapy, information on the patient's radiotherapy appointments and details of any visits to a health professional that the patient has made during their course of radiotherapy and during the period up to 8 weeks after the end of their radiotherapy.

For those patients randomised to receive no radiotherapy to the chest wall, but received post-operative chemotherapy, the patient diary will collect information about any visits the patient has made to a health professional during the first five months following the patient completing their post-operative chemotherapy.

For those patients randomised to receive no radiotherapy to the chest wall and received surgery and hormonal therapy alone OR neoadjuvant systemic therapy and surgery +/- postoperative hormonal therapy, the patient diary will collect information about any visits the patient has made to a health professional during the first five months following the date of the patient's last definitive surgery (mastectomy or axillary clearance). The five month period for those patients not randomised to receive radiotherapy to the chest wall is estimated to be the equivalent time period to those patients randomised to receive radiotherapy to allow comparative analysis to be performed.

Effectiveness

In the event that health outcomes are generally better with irradiation, the key economic question is what is the cost of achieving these improved outcomes (and how does this compare with other potential uses of these resources). Cost-effectiveness will be assessed by calculating the incremental cost per life year gained and the incremental cost per additional quality-adjusted life-year (QALY). The EQ5D (EuroQol, <http://www.euroqol.org/>) will be used in order to quality-adjust survival (Brooks, 1996). This measure is widely used in economic evaluation and is readily collected using a self-completed questionnaire. It comprises five simple questions (mobility, self care, ability to undertake usual activities, pain/discomfort, and anxiety/depression) each with only three possible responses. The EQ5D will be given to patients in the quality of life study along with the other quality of life questionnaires, that is, at baseline and follow-up at one, two, five and ten years post-randomisation. QALYs will be estimated using an established set of EQ5D values (Dolan, 1997).

Resource use

An NHS perspective is adopted for the estimation of costs. The economic evaluation requires the following patient-level information: details of chest wall irradiation for patients in the irradiation arm; and subsequent breast cancer related use of health care resources by patients in both arms

Unit cost data is required for irradiation and subsequent resource use. Differences in future resource use will arise primarily if there are differences in recurrence rates. With respect to subsequent resource use it is differences in resource use which matter, rather than the total cost. Thus it will only be necessary to collect unit cost data for those elements of health care that differ between the two arms. Detailed costing will be undertaken initially in two or three centres in order to develop a protocol to be applied in all centres. Towards the end of the study detailed patient-level information on the use of health care resources will be combined with the centre-specific unit costs.

Analysis

A particular feature of this trial is the large number of centres. Multilevel modelling will be used to take account of the clustering of cost data by centre (Manca et al., in press).

Patient-specific information on quality of life and survival will then be used to estimate the difference between arms in terms of QALYs and this will be related to the cost data in order to estimate the incremental cost per additional QALY.

For the purposes of cost-effectiveness analysis the appropriate time horizon is the lifetime of the patients. Thus the data collected during the five year follow-up of patients will be used to extrapolate the QALY difference between the arms.

Finally the sensitivity of the results to key parameters will be assessed (Briggs et al., 2002), and cost-effectiveness acceptability curves will be plotted to demonstrate the likelihood that a particular intervention is cost-effective for a range of monetary valuations of additional QALYs (Fenwick et al., 2004).

Informed consent and ethical issues

Ethical approval for the Health Economics substudy will be obtained at the same time as submitting the main trial protocol. The local investigator is responsible for obtaining each patient's signed informed consent prior to receiving the Health Economics substudy patient diary.

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Appendix I

Patient information sheet (main trial and TRANS-SUPREMO)

Invitation to participate in the SUPREMO trial

Patient Information Sheet

We would like to invite you to take part in the SUPREMO breast cancer trial (Selective Use of Postoperative Radiotherapy after Mastectomy). The SUPREMO trial aims to establish the benefits of postoperative radiotherapy to the chest wall in patients such as yourself who are at intermediate risk of recurrence. To help you decide if you would like to take part, please read this information sheet. It gives you details of what will be involved if you decide to take part in the trial, and also who to contact if you would like to discuss any aspect of the trial. A glossary of medical terms and words used in clinical trials is also included at the back of this leaflet.

Introduction to Clinical Trials

Great progress in the treatment of cancer has been possible through medical research. One of the most crucial aspects of this research is the participation of people like yourself.

A clinical trial is a study involving people and is designed to answer questions such as -

- Is there a better way of administering an existing treatment?
- Is the new approach better than the current procedure?
- Are there any side effects/ long term effects?

Carrying out clinical trials is the only sure way to evaluate as accurately as possible the real benefits and risks of a new treatment.

More than 14% cancer patients participate in cancer trials (Cancer Research UK, 2006)

Strict controls govern how clinical trials are conducted. Any research within the NHS that involves people, their tissue or data must have prior approval of the appropriate ethics committee. The primary responsibility of the ethics committee is the welfare and safety of individual research participants.

Sometimes the medication used in a clinical trial is not “new”, it is simply being used in a different way. In other cases, as with radiotherapy, the treatment has already been shown to be effective and safe for patients. Here researchers are looking at the outcomes of the trial to see what treatment works best for patients. This will allow doctors to improve cancer treatments for future patients.

Background to SUPREMO Trial

You have recently been diagnosed with breast cancer that has been completely removed by surgery. Anti-cancer drugs in the form of chemotherapy or hormonal therapy (or a combination of both) will also be given as part of your treatment. Another therapy that is currently offered to some patients with your type of cancer is radiotherapy to treat the site of your recent operation to remove your breast (mastectomy). Radiotherapy treats breast cancer using high energy x-rays to destroy the cancer cells and the aim of radiotherapy is to reduce the risk of the tumour coming back. In addition, when given in conjunction with anti-cancer drug treatment, it may also improve long-term survival. Postoperative radiotherapy is routinely given to patients at higher risk of recurrence than you (for example when 4 or more lymph nodes under the armpit are involved or the tumour is large). In patients (such as yourself) where there are less than 4 lymph nodes involved by cancer or there are no lymph nodes involved but there are other features of the cancer which increase the risk of the cancer recurring, it is not clear whether postoperative radiotherapy is needed.

Currently, there is wide variation in the use of radiotherapy across the UK and internationally, for patients in your risk group. The decision whether to give radiotherapy or not is generally based on local preference rather than established guidelines.

We would like to ask you to take part in our study to help us decide whether radiotherapy is helpful for women with your particular type of cancer. Your specialist has indicated that she or he thinks that you are suitable to take part in the SUPREMO study. Half of the patients in the trial will receive radiotherapy and half will not receive radiotherapy to the chest wall. In every other aspect the treatments will be the same. The trial will involve 1600 women.

What will I have to do if I take part?

If you agree to take part you will be asked to give your written consent to participate. To determine whether or not you will receive radiotherapy, your specialist will telephone the central office in Edinburgh that runs the SUPREMO trial.

The study office will check some details about you, your disease and the treatment you have been prescribed and will use a computer to allocate your treatment. You will have the same chance of receiving radiotherapy as not receiving it. Your specialist will be told whether you have been allocated a course of radiotherapy. You will also be seen in the hospital clinic for a routine examination following the completion of your radiotherapy or at an equivalent time if you are not allocated radiotherapy. You will subsequently be reviewed annually by a doctor, for at least 10 years, who will assess your medical condition. You will be asked particular questions in relation to the treatment that you have received. A breast X-ray (mammogram) of your other breast is recommended at least every two years for 10 years following your surgery. During the trial you may be asked to keep a record of all health services that you receive.

If you decide not to take part in the study you will receive the usual high standard treatment that is currently employed for patients with early breast cancer. You may be offered radiotherapy, if this is standard practice at your cancer centre, and you will be followed up at the surgical outpatient clinics in the usual way.

What does radiotherapy involve?

- Radiotherapy treats cancer using high energy x- rays in order to destroy the cancer cells, whilst doing as little harm as is possible to normal cells.
- Radiotherapy to the chest wall (the site of your mastectomy) is normally carried out over a period of 3 – 5 weeks, usually as an out patient.
- The detail of your radiotherapy planning and treatment will be discussed with you by a clinical/radiation oncologist.
- To plan your radiotherapy you will be asked to lie on a couch, then a series of measurements will be taken from your chest wall area by a team of radiographers. A CT scan may form part of the planning process. Planning usually takes around 20 – 40 minutes to complete.
- When you are treated you will be asked to lie on the couch so that the team of radiographers will be able to set you up in the same position as you were in at your planning session.
- A small dose of radiotherapy will be delivered to your chest wall from the treatment machine. Your specialist may in addition recommend radiotherapy on the same side to a part of the glandular area above your collarbone (known as the medial supraclavicular fossa) or to the glandular area beneath the breast bone (known as the internal mammary chain).
- The radiotherapy is normally given to the chest wall in a small dose each day. Treatments are given for about 10 – 15 minutes per day on week days. No treatment is given over the week ends.
- Radiation to the chest wall does not mean that you will not be considered suitable for a possible breast reconstruction. The surgeon will take into consideration the fact that tissue in this area has been irradiated when advising which reconstruction technique should be used.
- Furthermore, if breast reconstruction has already been performed at the time of the mastectomy operation (immediate reconstruction) then this does not mean that you will not be considered suitable for subsequent irradiation to the chest wall.
- Radiotherapy, after breast reconstruction (where an implant has been used) may, in the long term, cause the implant to harden and change shape as the result of the formation of scar tissue following the radiotherapy. This can be treated by removing the scar tissue and changing the implant at a later date.

What are the possible risks of taking part?

Like all treatments there may be side effects with radiotherapy. Radiotherapy may cause skin reactions leading to chest wall tenderness, redness and itching. These develop in the latter part of the course of radiotherapy and usually settle within one month of the treatment finishing. Chest wall pain, which is usually mild and intermittent, can occur. Rarely (less than 1% of patients), radiotherapy may cause a temporary inflammation of the lung causing shortness of breath which can last for a number of weeks in the first year of treatment, and occasionally long term. Rib

fractures may occur in the longer term (less than 1% of patients). Studies have shown that 10-30 years after radiation treatment there can be an increased chance of heart problems. For this reason the position of the heart in relation to the radiation fields is nowadays very carefully determined at the time of the treatment planning so that no, or as little as possible of heart tissue lies in the radiation fields. It should be emphasised that these serious complications are rare. The trial will look at the possible risks of radiotherapy over the ten year follow up period.

If you undergo breast reconstruction it is possible that radiotherapy to the chest wall may in the long-term cause some shrinkage of the breast.

The possible risk of not being given radiotherapy is that there may be a slightly higher chance of breast cancer returning compared to women who have received radiotherapy. However in women with 1-3 affected lymph nodes or non-involved lymph nodes but other risk factors for local recurrence and the type of surgery that you have had, the chances of the disease recurring at the site of your operation are small. If the disease did recur at the site of your mastectomy, a course of radiotherapy to your chest wall would be considered.

Are there any benefits to taking part?

Radiotherapy reduces the risk of recurrence of the cancer in the area where you have had surgery and might improve your life expectancy. Whether or not you decide to take part in the study you will receive the highest standards of care. You will have increased contact with specialist nurses. The information that we get from the study will help us gain knowledge about the best way of treating breast cancer. It will help us to measure the advantages of radiotherapy in women with the type of breast cancer that you have.

Pathology Examination

After your operation, the breast tissue and any lymph nodes removed were examined in the laboratory in order to determine the type of tumour and any spread. The results of this examination, and the consequences for your further treatment, have already been discussed with you. Part of the tumour that has been removed is kept in the pathology archive in a small block. If it is ever needed in the future, these blocks can be used again to do new tests on the tumour tissue. An independent trials pathologist, based at a central laboratory in the UK or the Netherlands, will examine a small sample of the breast tissue taken during your operation. This will allow the central pathologist to compare their review of the tissue with the one done at the time of your operation by the pathologist at your local hospital. This examination of the pathology reporting will involve sending one of the blocks containing your breast tissue to the central laboratory. After the review of the tissue by the central pathologist, the tissue block will be returned to your hospital. In addition, if you received chemotherapy or hormone therapy before your surgery, a small piece of tissue taken at the time of the original diagnosis will also be requested and examined as described above.

TRANS-SUPREMO

If you agree to be entered into the SUPREMO trial we would like to do some further research on your breast cancer tissue. With your permission we would like to send a part of your breast cancer to a central laboratory where we can analyse the tissue for some special molecular features. We would also like to retain a tiny piece of your breast cancer tissue and use this in the future for research to help understand more

about breast cancer and radiotherapy treatments. After removing this sample we will return the rest of the cancer tissue to your hospital. Tissue would be stored in a way such that it would not be identifiable and no one would be informed about specific findings relating to you. For those patients who experience a recurrence of their cancer or develop a cancer in their other breast, we would also like to store samples of this tissue, if available, as outlined above.

We do not at present know all the molecular markers or genes we will be looking at but the tissue we collect could be analysed for the presence of many different proteins and genes inside the breast cancer cells. We will be looking at particular proteins or genes that we think might help improve our ability to treat breast cancer and in particular to help predict if some cancers are best treated with radiotherapy, whilst others are not. Because the samples are not identifiable results of this research will have no influence on your treatment but doctors taking part in the study will be informed of the general findings of this research. If you do not want your tissue used in this way please tell us. You can still take part in the main trial.

We would also like to do further research on your blood, including your genetic information (DNA). Recently we have become aware that some people have a particular profile of genes or proteins in their blood which mean they respond better to different forms of cancer therapy or which can identify if their cancer is more likely to recur. We need to do further research to identify those genes or proteins which might be important in this study. With your permission we would like to send a sample of your blood to a central laboratory where we can analyse it for genes (using your DNA) or proteins. We would collect no more than the equivalent of 2 tablespoons of blood when you first enter the study and, for those who experience a recurrence of their cancer, the same amount at the time of this recurrence. Your blood and DNA would be stored in a way such that it would not be identifiable and no one would be informed about specific findings relating to you.

Because the samples are not identifiable, results of this research will have no influence on your treatment, nor will anyone be able to access them, but doctors taking part in the study will be informed of the general findings of this research. If you do not want your blood or DNA used in this way please tell us. You can still take part in the main trial.

It is possible that other scientists or doctors may want to use this material to improve diagnosis and treatment of cancer, but their request will have to be considered and approved by an ethics committee before they are allowed to do so.

Tumour and other material collected during this study will not be sold to third parties or used for commercial gain. Intellectual property rights (knowledge gained from the trial) that may arise as a result of findings from this research could be exploited commercially. The rights to any intellectual property will reside with the investigators.

Do I have to take part?

No, taking part is voluntary. If you would prefer not to take part you do not have to give a reason. Your doctor would not be upset and your treatment would not be affected. If you take part but later change your mind you can withdraw from the study at any time without giving a reason and without hindrance or detriment to your future treatment. We will give you a copy of your consent form to keep.

Confidentiality

All the study data will be confidential to the research team. You will not be identified in any published study results. All study data will be handled under the auspices of the MRC- Trial Management Group and treated confidentially in compliance with the Data Protection Act (1998).

What do I do now?

You will be contacted by a member of the research staff in a day or so. Please let him/her know if you are interested in taking part.

We would want to inform your General Practitioner that you are taking part in the trial.

Thank you very much for considering taking part in our research. Please discuss this information with your family, friends or GP if you wish.

Prof. Ian Kunkler Chief Investigator, SUPREMO trial

Local contact name(s) and phone number(s):

If you would like to speak to a doctor who is independent of the trial, please contact:

Appendix II Informed consent form (main trial and TRANS-SUPREMO)

SUPREMO breast cancer trial

Selective Use of Postoperative Radiotherapy after Mastectomy

Informed Consent Form

Patient identification number for this trial:.....

Name of patient:

Name of clinician

Hospital:

Please initial boxes

1. I have read and understood the patient information sheet provided and have had sufficient time to decide whether to take part in both the clinical trial and research study (TRANS-SUPREMO). I have had the opportunity to ask questions and consider the answers given.
2. I understand that participation in the trial is voluntary and that I may withdraw from the trial at any time of my own accord and without giving any reason and without my medical care or legal rights being affected.
3. I understand that sections of any of my medical notes may be looked at by research staff from the Information Services Division (ISD) Cancer Clinical Trials Team, and other collaborating UK Clinical trials units for the purpose of data monitoring, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.
4. I understand that data will be passed to the ISD Cancer Clinical Trials Team and that this information will include my name, date of birth, hospital number and NHS number (or Community Health Index number) from which it is possible to identify me as an individual.
5. I agree that my General Practitioner will be informed of my participation in this study and will be advised of any clinically significant information that comes to light.
6. I understand that a small sample of my breast tissue taken during my surgery and, if I received chemotherapy or hormone therapy prior to surgery, as part of my original diagnosis will be sent to a central laboratory for review.

☐☐☐☐☐☐

I confirm that I have explained the nature of this trial and the research study (TRANS-SUPREMO) to the above named patient and that she has understood the explanation given to her.

Clinician's signature:..... **Date:**.....

I hereby freely give my consent to take part in the SUPREMO trial

Patient's signature: **Date:**.....

I hereby freely give my consent to take part in the TRANS-SUPREMO study
and I donate:

tumour tissue	<input type="checkbox"/>	
serum/plasma	<input type="checkbox"/>	(Please initial boxes)
and DNA	<input type="checkbox"/>	

for these studies. (We will only be able to collect material if you initial these boxes.)

Patient's signature: **Date:**.....

(A separate signature for TRANS-SUPREMO is required for legal reasons).

Signature on this form does not affect your legal rights, you may take part in the main trial and decline to take part in the TRANS-SUPREMO research study.

4 copies of consent form required: 1 original for patient, 1 original for researcher (to be kept in site file), 1 copy for trials office, 1 copy to be kept with hospital notes.

Glossary Of Terms

Anthracycline: A type of chemotherapy drug used to lessen the risk of recurrence.

Breast tissue: A complicated arrangement of tissues closely tied to nerves, blood vessels and fatty tissues.

Breast reconstruction: A procedure to reshape a woman's breast after mastectomy.

Cancer: A group of diseases in which malignant cells grow out of control and spread to other parts of the body.

Chemotherapy: Is the use of anti-cancer drugs to destroy cancer cells.

Clinical oncologist/ radiation oncologist: A person who specialises in treating cancer with radiation.

Clinical trial: A scientific test of the effectiveness and safety of a particular treatment using consenting human participants.

CT: (Computed tomography) scan. An imaging technology which uses a computer to assemble multiple x-ray images into a cross-section image of the head or the body.

Diagnosis: Process of identifying a disease from symptoms and tests.

DNA: Deoxyribonucleic acid is a nucleic acid that contains genetic instructions used in the development and functioning of all known living organisms.

Hormonal Therapies: Act by altering the production or activity of particular hormones in the body.

Mammogram: A low-dose x-ray of the breast to check for any abnormal tissue.

Mastectomy: Surgical removal of all or part of the breast.

Medical oncologist: A person who specialises in treating cancer with drugs.

Radiographer: A healthcare professional who takes x-rays and scans (diagnostic radiographer) or gives radiotherapy (therapeutic radiographer)

Radiotherapy: Treatment of disease by x-rays.

Randomisation: The treatment each patient receives is determined "by chance" (using a computer)

Appendix III

Patient information sheet (Quality of Life and Health Economics substudies)

Invitation to participate in the SUPREMO trial Quality of Life and Health Economics substudies

Patient Information Sheet

We would like to invite you to take part in the SUPREMO (Selective Use of Postoperative Radiotherapy after Mastectomy) Quality of Life and Health Economics substudies. To help you decide if you would like to take part, please read this information sheet. It gives you details of what will be involved if you decide to take part in the trial, and also who to contact if you would like to discuss any aspect of the trial.

As part of the SUPREMO trial we are asking women to fill in questionnaires so that we can learn about the effects of treatment in more detail. Your specialist has indicated that s/he thinks that you are suitable to take part in the SUPREMO Quality of Life and Health Economics substudies.

What will I have to do if I take part?

Quality of Life substudy

If you agree, you will be asked to complete a questionnaire before starting your treatment and again one year, two years, five years and ten years later. The questionnaires will be explained to you on the first occasion by a member of staff who will answer any questions you have about how to fill it in.

The questionnaires have been carefully developed with the help of doctors, nurses and women like yourself. They contain questions about a range of physical symptoms and activities, your emotional wellbeing and other aspects of your everyday life. We also want to know how you feel about your appearance after treatment to the chest wall and any side effects you experience. There are no 'right' or 'wrong' answers – we simply want to find out about the experience of treatment for women in this trial. Each questionnaire will take about 30 minutes to complete.

In addition, as part of the assessment of the cost effectiveness of radiotherapy in the trial we would like you to complete, at the same time as the quality of life assessments, a short questionnaire known as EQ5D. This has 5 questions on mobility, self care, ability to undertake usual activity, pain/discomfort and mood. The questionnaire takes only a few minutes to complete. This additional information will allow us to take account of the quality of life of patients in the overall economic evaluation of radiotherapy after a mastectomy.

Health Economics substudy

If you agree, you will be asked to complete a patient diary colour coded to match your treatment and whether you received post-operative chemotherapy. If you are randomised to receive radiotherapy and received post-operative chemotherapy, you will receive a red booklet where you will be asked to record information about your radiotherapy appointments and details of any visits to a health professional during the

period following your post-operative chemotherapy and the start of your radiotherapy, during your course of radiotherapy and during the period up to 8 weeks after the completion of your radiotherapy. If you are randomised to receive radiotherapy and received surgery and hormonal therapy alone OR neoadjuvant systemic therapy and surgery +/- postoperative hormonal therapy, you will receive an orange booklet where you will be asked to record information about your radiotherapy appointments and details of any visits to a health professional during the period following the date of your last surgery and the start of your radiotherapy, during your course of radiotherapy and during the period up to 8 weeks after the completion of your radiotherapy.

If you are randomised to not receive radiotherapy, but did receive post-operative chemotherapy, you will receive a blue booklet where you will be asked to record any visits to a health professional during the first five months following the completion of your post-operative chemotherapy. If you are randomised to not receive radiotherapy and received surgery and hormonal therapy alone OR neoadjuvant systemic therapy and surgery +/- postoperative hormonal therapy, you will receive a green booklet where you will be asked to record any visits to a health professional during the first five months following the date of your last surgery (either mastectomy or axillary clearance).

The Health Economics substudy will allow us to capture certain aspects of the costs associated with your treatment, both to organisations like the NHS and to you personally.

Are there any benefits to taking part?

The opportunity for interaction with a trials/research nurse can be considered a benefit.

Do I have to take part?

No, taking part is voluntary. If you would prefer not to take part you do not have to give a reason. Your doctor would not be upset and your treatment would not be affected in any way. If you take part, but later change your mind, you can withdraw from the study at any time without giving any reason and without hindrance or detriment to your future treatment. We will give you a copy of your consent form to keep.

Confidentiality

All the study data will be confidential to the research team. You will not be identified in any published study results. All study data will be handled under the auspices of the MRC- Trial Management Group and treated confidentially in compliance with the Data Protection Act (1998).

What do I do now?

You will be contacted by a member of the research staff in a day or so. Please let him/her know if you are interested in taking part.

We would want to inform your General Practitioner that you are taking part in these studies. If the scores on The Hospital Anxiety and Depression (HAD) scale within the Quality of Life study suggest that you are distressed then we will inform your GP.

Thank you very much for considering taking part in our research. Please discuss this information with your family, friends or GP if you wish.

Prof. Ian Kunkler

Chief investigator, SUPREMO trial

Local contact name(s) and phone number(s):

If you would like to speak to a doctor who is independent of the trial, please contact:

Appendix IV Informed consent form (Quality of Life and Health Economics substudies)

SUPREMO breast cancer trial

Selective Use of Postoperative Radiotherapy after Mastectomy

Quality of Life and Health Economics studies Informed Consent Form

Patient identification number for this trial:.....

Name of patient:

Name of clinician

Hospital:

Please initial boxes

1. I have read and understood the Quality of Life and Health Economics patient information sheet provided and have had sufficient time to decide whether to take part in these studies. I have had the opportunity to ask questions and consider the answers given. ☐
2. I understand that participation in these studies is voluntary and that I may withdraw at any time of my own accord and without giving any reason and without my medical care or legal rights being affected. ☐
3. I agree that my General Practitioner will be informed of my participation in these studies and will be advised of any clinically significant information that comes to light. ☐
4. I agree to researchers from the Centre of Population Health Sciences, the University of Edinburgh telephoning my GP to confirm I am fit and well to receive Quality of Life questionnaire booklets to be sent out by post. I understand that my full name and address will be collected for this purpose only. ☐

I confirm that I have explained the nature of this study to the above named patient and that she has understood the explanation given to her.

Clinician's signature:.....Date:.....

I hereby freely give my consent to take part in the SUPREMO quality of life study.

Patient's signature: Date:.....

I hereby freely give my consent to take part in the SUPREMO health economics study.

Patient's signature: **Date:**.....

(Signature on this form does not affect your legal rights. You may take part in the main trial and decline to take part in the Quality of Life substudy. You may also take part in the Quality of Life substudy and not the Health Economics substudy and vice versa)

4 copies of consent form required: 1 original for patient, 1 original for researcher (to be kept in site file), 1 copy for trials office, 1 copy to be kept with hospital notes.

Appendix V

Patient information sheet (Cardiac substudy)

Invitation to participate in the SUPREMO trial Cardiac sub-study

Patient Information Sheet

We would like to invite you to take part in the SUPREMO breast cancer trial (**Selective Use of Postoperative Radiotherapy after Mastectomy**) cardiac sub-study. To help you decide if you would like to take part, please read this information sheet. It gives you details of what will be involved if you decide to take part in the cardiac substudy, and also who to contact if you would like to discuss any aspect of the substudy.

The main SUPREMO trial aims to find out if chest wall radiotherapy is beneficial after mastectomy, chemotherapy and/or hormone treatments. The cardiac substudy aims to assess a new way to detect possible damage to the heart that can result from these treatments using a blood test called BNP (B-type natriuretic peptide). This is the first study to investigate the effect of chemotherapy and radiotherapy, alone or in combination, on the heart. If you do agree to take part in this sub-study we need your agreement to take part after surgery and before starting chemotherapy (if applicable). We would also like to approach you about taking part in the main SUPREMO trial and the TRANS-SUPREMO and Quality of Life substudies. We may do this now or, if you do not want to think about taking part in the main trial or other substudies now, later on towards the end of your course of chemotherapy.

Introduction

Radiotherapy reduces the risk of recurrence of the cancer in the area where you have had surgery and might improve your life expectancy. Like many treatments radiotherapy and chemotherapy have side effects, both short term and long term. One of the potential long-term side effects of radiotherapy for breast cancer and of certain forms of chemotherapy (known as anthracyclines) is damage to the heart. It should be emphasised that this complication is rare. The total doses of anthracyclines are limited to reduce the risk of cardiac damage. Where possible the dose to the heart from radiotherapy is also limited. However, we have relatively little information on the frequency of cardiac damage in patients receiving either radiotherapy or anthracycline chemotherapy alone, or together. The SUPREMO cardiac substudy will help us to collect this information.

Conventionally, damage to the heart is detected by measuring the electrical activity of the heart. This is known as an electrocardiogram (or ECG). An ECG is a non-invasive painless test. It involves placing small adhesive pads temporarily to your chest and recording the electrical activity of your heart. It takes only a few minutes.

The pumping action of the heart can also be assessed by passing sound waves through the heart. This is known as echocardiography. This test takes around 30-45 mins. More recently B type natriuretic peptide (BNP), a chemical substance produced by the heart when it is damaged, has been used to assess the health of the heart. BNP can be measured on a simple blood test. In this research study we will be assessing the value of BNP and other blood measurements in detecting any damage to the heart at the earliest possible stage.

What will I have to do if I take part?

If you agree to take part in this study, you will be asked about any cardiac symptoms (such as chest pain), family history of heart disease, risk factors for heart disease (such as smoking, high blood pressure, high cholesterol) and your height, weight, pulse rate and blood pressure will be recorded. You will be asked to have a blood test for BNP (and other blood measurements of cardiac damage). You will also have an ECG and an echocardiogram on entry to the study. These tests will be repeated at one, five and 10 years after surgery and for those patients who experience a recurrence of their breast cancer or develop a cancer in their other breast, these tests will be repeated at the time of the recurrence/ new diagnosis.

If you **have chemotherapy**, an additional 2 clinic visits will be required to take blood for BNP (and other blood measurements of cardiac damage). These will be:

1. within 3 weeks of completing chemotherapy and before radiotherapy (if given) starts.
2. on completion of radiotherapy or 3 months after chemotherapy if no radiotherapy is given.

If you **do not have chemotherapy**, 1 additional clinic visit will be required to take blood for BNP (and other blood measurements of cardiac damage). This will be: on completion of radiotherapy or 3 months after surgery if no radiotherapy is given. At each of these visits we would collect no more than the equivalent of 2 teaspoons of blood.

If the level of BNP rises significantly, we will notify your oncologist, and recommend to him/her that you have an echocardiogram and ECG to give us further information about the function of your heart. A copy of your ECG and echocardiogram will be sent to the study team for assessment. If your ECG or echocardiogram or blood test are abnormal you will be referred to a heart specialist for further assessment and possible treatment.

Are there any risks to participating in the study?

We do not anticipate any side effects relating to the blood test for BNP or to measuring your heart function.

Are there any benefits to taking part?

The information that we obtain from the study will help us gain knowledge about the impact of cancer treatment on your heart. You will have regular monitoring of how your heart is working. You will have increased contact with specialist nurses.

Do I have to take part?

No, taking part is voluntary. We would encourage women who agree to this sub-study to go on to take part in the main SUPREMO trial, but this is also voluntary. If you would prefer not to take part you do not have to give a reason. Your doctor would not be upset and your treatment would not be affected in any way. If you take part but later change your mind you can withdraw from the study at any time without giving a reason and without hindrance or detriment to your future treatment. We will give you a copy of your consent form to keep.

Confidentiality

All the study data will be confidential to the research team. You will not be identified in any published study results. All study data will be handled under the auspices of the MRC- Trial Management Group and treated confidentially in compliance with the Data Protection Act (1998).

What do I do now?

You will be contacted by a member of the research staff in a day or so. Please let him/her know if you are interested in taking part.

We would want to inform your General Practitioner that you are taking part in this study.

Thank you very much for considering taking part in our research. Please discuss this information with your family, friends or GP if you wish.

Prof. Ian Kunkler Chief Investigator, SUPREMO trial

Local contact name(s) and phone number(s):

If you would like to speak to a doctor who is independent of the study, please contact:

Appendix VI Informed consent form (Cardiac substudy)

SUPREMO breast cancer trial

Selective Use of Postoperative Radiotherapy after Mastectomy

Cardiac Substudy

Informed Consent Form

Patient identification number for this trial:.....

Name of patient:

Name of clinician

Hospital:

Please initial boxes

1. I have read and understood the Cardiac Study patient information sheet provided and have had sufficient time to decide whether to take part in this study. I have had the opportunity to ask questions and consider the answers given. ☐
2. I understand that participation in the study is voluntary and that I may withdraw at any time of my own accord and without giving any reason and without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by research staff from the Information Services Division (ISD) Cancer Clinical Trials Team, and other collaborating UK Clinical trials units for the purpose of data monitoring, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐
4. I agree that my General Practitioner will be informed of my participation in this study and will be advised of any clinically significant information that comes to light. ☐
5. I agree to donate serum/plasma for this study which will be stored for future research to learn about, prevent or treat cancer. ☐

For those who wish to enter the Cardiac study only at present:

6. I agree to be approached towards the end of my chemotherapy about entering the main SUPREMO radiotherapy trial and TRANS SUPREMO and Quality of Life substudies.

☐

7. I agree to baseline data and details of my cancer treatments being collected for the purposes of the trial even if I decide not to enter the main SUPREMO trial and other substudies at the end of my chemotherapy.

☐

I confirm that I have explained the nature of this study to the above named patient and that she has understood the explanation given to her.

Clinician's signature:..... **Date:**.....

I hereby freely give my consent to take part in the SUPREMO cardiac study.

Patient's signature: **Date:**.....

(Signature on this form does not affect your legal rights, you may take part in the main trial and decline to take part in this part of the trial)

4 copies of consent form required: 1 original for patient, 1 original for researcher (to be kept in site file), 1 copy for trials office, 1 copy to be kept with hospital notes.

Appendix VII Letter to general practitioner covering main trial and sub-studies

Dear Colleague,

SUPREMO trial (Selective Use of Postoperative Radiotherapy after Mastectomy)

I am writing to let you know that your patient:

Mrs/Ms.....
of

has agreed to take part in an international Phase III randomised trial (SUPREMO) to assess the role of postoperative chest wall irradiation after mastectomy and axillary surgery for breast cancer. Eligibility is restricted to women with intermediate risk breast cancer (ie with 1-3 histologically involved nodes or histologically negative nodes with high grade histology and/or lymphovascular invasion). (Neo)adjuvant systemic therapy with chemotherapy and/or endocrine therapy is given as appropriate. The value of adjuvant chest wall irradiation in this group of patients is uncertain and at present this is not standard therapy. In women with > 4 involved nodes there is good evidence that loco-regional irradiation after mastectomy given with systemic therapy improves overall survival. However the role of loco-regional irradiation in women at lower risk of loco-regional recurrence is unclear. The recent guidance from the UK National Institute for Clinical Excellence (NICE; 2009) encourages recruitment of patients with intermediate risk breast cancer after mastectomy into the SUPREMO trial.

The trial aims to assess whether the addition of radiotherapy will improve overall survival in women at intermediate risk of recurrence. In addition we will be assessing the impact of chest wall irradiation on quality of life, cardiac morbidity and use of health service resources. Medical history and examination will be conducted on entry to the study, after radiotherapy (if given) or at an equivalent time point if no radiotherapy is given and annually for 10 years. A mammogram of the opposite breast, if appropriate, is recommended at least in alternate years for 10 years from the date of mastectomy.

Sub-studies

(please note that participation in sub studies is optional and requires separate informed consent).

a) Cardiac substudy

The primary aim of the cardiac sub study is to assess the utility of B type natriuretic peptide (BNP) in identifying and predicting cardiac toxicity in patients undergoing adjuvant radiotherapy and/or chemotherapy. Cardiac risk factors, including measurement of serum cholesterol, will be documented by a doctor/research nurse at baseline. Blood levels of BNP will be measured in conjunction with electrocardiography (ECG) and echocardiography. If cardiac symptoms or signs warrant or BNP rises significantly above threshold levels patients will be referred for additional cardiac assessment to a cardiologist. The last BNP measurement along with a further clinical cardiac assessment and ECG will be carried out at 10 years after surgery.

b) TRANS-SUPREMO translational research substudy

In TRANS-SUPREMO tissue microarrays will be constructed from pathological blocks for subsequent identification of a molecular signature of radiosensitivity and relapse. We will also collect whole blood, serum and plasma at randomisation, recurrence (local and/or distant relapse) and/or development of a contralateral breast primary to look for pharmacogenetic and protein markers of relapse/outcome.

c) Quality of life substudy

The patient will complete Quality of Life assessment questionnaire booklets before randomisation and at 1, 2, 5 and 10 years post-mastectomy. The baseline assessment will be completed in the clinic, and subsequent questionnaire booklets will be posted to the patient's home. A member of the Centre for Population Health Sciences, the University of Edinburgh will contact your practice in advance of sending out the questionnaires to confirm that the patient is alive and well enough to receive the booklet.

d) Health Economics substudy

The patient will complete a patient diary received on entry into the study by a hospital staff member. The diary will capture aspects of the costs associated with the patient's treatment both to organisations such as the NHS and to the patient themselves.

The study has been approved by the Multi-centre Ethics Committee and your local ethical committee. It is anticipated that 1600 patients will be randomised over a six year recruitment period. A Data Monitoring Committee will meet at least six monthly to review study progress and safety. The final trial report will be submitted to a peer reviewed journal and this will be made available to you if requested.

If you have any questions about the trial, you may wish to contact Chief Investigator, Prof Ian Kunkler, or the local Principal Investigator:

Dr

Address:.....

.....

Tel:Email:

Yours sincerely,

Prof Ian Kunkler on behalf of the SUPREMO trial study team

Prof Ian Kunkler, Consultant in Clinical Oncology, University Department of Clinical Oncology, Western General Hospital, University of Edinburgh, Crewe Road, Edinburgh, EH4 2XU. Telephone +44 (0)131 537 2214; Fax:+44 (0)131 275 7512

Appendix VIII

RTOG/EORTC acute radiation morbidity scoring system

Organ	0	1	2	3	4
Skin	No change over baseline	Follicular, faint or dull erythema/ epilation/ dry desquamation/decreased sweating	Bright erythema, patchy moist desquamation/moderate oedema	Confluent moist desquamation other than skin folds, pitting oedema	Ulceration, haemorrhage, necrosis
Lung	No change	Mild symptoms of dry cough or dyspnoea on exertion	Persistent cough requiring narcotic, anti-tussive agents/dyspnoea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnoea at rest/clinical or radiological evidence of acute pneumonitis/ intermittent oxygen or steroids may be required	Severe respiratory insufficiency/ continuous oxygen or assisted ventilation
Heart	No change over baseline	Asymptomatic but objective evidence of ECG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with ECG changes and radiological findings of congestive heart failure or pericardial disease/no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to nonsurgical measures

RTOG/EORTC late radiation morbidity scoring system

Organ	0	1	2	3	4	5
Skin	None	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; total hair loss	Marked atrophy; gross telangiectasia	Ulceration	Death directly related to Radiation Late Morbidity
Lung	None	Asymptomatic or mild symptoms	Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; patchy radiographic changes	Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes	Severe respiratory insufficiency/ Continuous O2/Assisted Ventilation	Death directly related to Radiation Late Morbidity
Heart	None	Asymptomatic or mild symptoms; transient T wave inversion & ST change; sinus tachycardia > 110 (at rest)	Moderate angina on effort; Mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low ORS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; ECG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis	Death directly related to Radiation Late Morbidity
Bone	None	Asymptomatic. No growth; reduced bone density	Moderate pain or tenderness; growth retardation; irregular sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/Spontaneous fracture	Death directly related to Radiation Late Morbidity

Appendix IX TNM Clinical Classification

T - Primary tumour

TX: Primary tumour cannot be assessed

T0: No evidence of primary tumour

Tis: Carcinoma in situ,
Tis (DCIS): Ductal carcinoma in situ
Tis (LCIS): Lobular carcinoma in situ
Tis (Paget): Paget's disease of the nipple with no tumour.

Note: Paget disease associated with a tumour is classified according to the size of the tumour.

T1: Tumour 2.0 cm or less in greatest dimension
T1mic: Microinvasion 0.1 cm or less in greatest dimension

Note: Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all individual foci.) The presence of multiple foci of microinvasion should be noted, as it is with multiple larger invasive carcinomas.

T1a: More than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b: More than 0.5 cm but not more than 1.0 cm in greatest dimension
T1c: More than 1.0 cm but not more than 2.0 cm in greatest dimension

T2: Tumour more than 2.0 cm but not more than 5.0 cm in greatest dimension

T3: Tumour more than 5.0 cm in greatest dimension

T4: Tumour of any size with direct extension to chest wall or skin, only as described in T4a to T4d

Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.

T4a: Extension to chest wall
T4b: Oedema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c: Both 4a and 4b above
T4d: Inflammatory carcinoma

Note: Inflammatory carcinoma of the breast is characterised by diffuse, brawny induration of the skin with an erysipeloid edge, usually with no underlying mass. If the skin biopsy is negative and there is no localised measurable primary cancer, the T category is pTX when pathologically staging a clinically inflammatory carcinoma (T4d). Dimpling of the skin, nipple retraction, or other skin changes, except those in T4b and T4d, may occur in T1, T2, or T3 without affecting the classification.

N - Regional lymph nodes

NX: Regional lymph nodes cannot be assessed (e.g., previously removed)

N0: No regional lymph node metastasis

N1: Metastasis in movable ipsilateral axillary lymph node(s)

N2: Metastasis in fixed ipsilateral axillary lymph node(s), or in clinically apparent* ipsilateral internal mammary lymph node(s) in the *absence* of clinically evident axillary lymph node metastasis

N2a: Metastasis in axillary lymph node(s) fixed to one another or to other structures

N2b: Metastasis only in clinically apparent* internal mammary lymph nodes and in the absence of clinically evident axillary lymph node metastasis

N3: Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or, metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a: Metastasis in infraclavicular lymph node(s)

N3b: Metastasis in internal mammary and axillary lymph node(s)

N3c: Metastasis in supraclavicular lymph node(s)

* [Note: Clinically apparent = detected by clinical examination or by imaging studies (excluding lymphoscintigraphy).]

M - Distant metastasis

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

pTNM Pathological classification

pT – Primary Tumour

The pathological classification requires the examination of the primary carcinoma with no gross tumour at the margins of resection. A case can be classified pT if there is only microscopic tumour in a margin.

The pT categories correspond to the T categories.

Note: When classifying pT the tumour size is a measurement of the invasive component. If there is a large in situ component (eg 4cm) and a small invasive component (eg 0.5cm), the tumour is coded pT1a.

PN – Regional Lymph nodes

The pathological classification requires the resection and examination of at least the low axillary lymph nodes (level I). Such a resection will ordinarily include 6 or more

lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.

Examination of one or more sentinel lymph nodes may be used for pathological classification. If classification is based solely on sentinel node biopsy without subsequent axillary lymph node dissection it should be designated (sn) for sentinel node, eg pN1(sn).

pNX: Regional lymph nodes cannot be assessed (not removed for study or previously removed)

pN0: No regional lymph node metastasis*

[Note: *cases with only isolated tumour cells (ITCs) in regional lymph nodes are classified as pN0. ITC are single tumour cells or small clusters of cells not more than 0.2 mm in greatest dimension, that are usually detected by immunohistochemistry or molecular methods but which may be verified on H&E stains. ITCs do not typically show evidence of metastatic activity, e.g., proliferation or stromal reaction.]

pN1mi: Micrometastasis (larger than 0.2 mm but none larger than 2.0 mm in greatest dimension)

pN1: Metastasis in 1 to 3 ipsilateral axillary lymph node(s), and/or in ipsilateral internal mammary nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent**

pN1a: Metastasis in 1 to 3 axillary lymph node(s), including at least one larger than 2mm in greatest dimension.

pN1b: internal mammary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent**

pN1c: Metastasis in 1 to 3 axillary lymph nodes and internal mammary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent.

pN2: Metastasis in 4 to 9 ipsilateral axillary lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph node(s) in the absence of axillary lymph node metastasis

** [Note: Not clinically apparent = not detected by clinical examination or by imaging studies (excluding lymphoscintigraphy)]

* [Note: Clinically apparent = detected by clinical examination or by imaging studies (excluding lymphoscintigraphy) or grossly visible pathologically]

pN2a: Metastasis in 4 to 9 axillary lymph nodes including at least one that is larger than 2.0 mm)

pN2b: Metastasis in clinically apparent internal mammary lymph node(s) in the *absence* of axillary lymph node metastasis

pN3: Metastasis in 10 or more ipsilateral axillary lymph nodes; or in ipsilateral infraclavicular lymph nodes; or in clinically apparent ipsilateral internal mammary lymph node(s) in the *presence* of one or

more positive axillary lymph nodes; or, in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or, in ipsilateral supraclavicular lymph nodes

pN3a: Metastasis in 10 or more axillary lymph nodes (at least one larger than 2.0 mm) or, metastasis in infraclavicular lymph nodes

pN3b: Metastasis in clinically apparent internal mammary lymph nodes in the *presence* of positive axillary lymph node(s); or, metastasis in more than 3 axillary lymph nodes *and* in internal mammary lymph nodes with microscopic metastasis detected by sentinel lymph node dissection but not clinically apparent

pN3c: Metastasis in supraclavicular lymph node(s)

pM – Distant Metastasis

The pM categories correspond to the M categories.

Source: UICC TNM Classification of Malignant Tumours Sixth Edition 2002 Edited by L.H.Sobin and Ch. Wittekind

Additional Descriptors

In addition to c and p to designate clinical or pathological stage further information can be used by the use of optional descriptors for example:

y

If patients receive neoadjuvant therapy prior to surgery or radiotherapy the TNM may not be same as if no neoadjuvant treatment was given. To overcome this problem the additional descriptor y can be used as a prefix to indicate the extent of disease at the time of assessment even if multimodality therapy has already commenced (i.e., yT1N0M0 means that the patient was staged following neoadjuvant treatment, and the anatomic extent of disease at that time was confined to the primary site, and of a size commensurate with the T1 category for that tumour type).

Source: UICC (2009). How to use the TNM Classification, accessed July 21 2009 from http://www.uicc.org/index.php?option=com_content&task=view&id=14296&Itemid=428

c

Clinical classification, designated cTNM or TNM. Clinical classification is based on evidence acquired before primary treatment. Clinical assessment uses information available prior to first definitive treatment including, but not limited to, physical examination, imaging, endoscopy, biopsy, and surgical exploration. Clinical stage is assigned prior to any cancer-directed treatment and is not changed on the basis of subsequent information. Clinical staging ends if a decision is made not to treat the patient. The clinical stage is essential to selecting and evaluating primary therapy.

Source: AJCC Comparison Guide: Fifth versus Sixth Edition, accessed August 19 2010 from <http://www.cancerstaging.org/products/ajccguide.pdf>.

Appendix X Collaborating Organisations

Contacts:

Anglo-Celtic Co-operative Oncology Group:
Prof. Robert C F Leonard

Borstkanker Onderzoeksgroep Nederland:
Dr. Nicola Russell

Central East European Oncology Group:
Prof. Jacek Jassem

Chinese Network of 9 Hospitals (under leadership of National Cancer Centre,
Academy of Medical Sciences, Beijing)
Prof. Yexiong Li and Associate Prof. Shulian Wang

European Organisation for Research and Treatment of Cancer:
Dr. Geertjan van Tienhoven

GECO Peru:
Dr. Henry Gomez Moreno

Hellenic Breast Surgical Society:
Prof. Christos Markopoulos

International Breast Cancer Study Group:
Prof. Aron Goldhirsch

Irish Clinical Oncology Research Group:
Dr. Brian Moulton

Japanese Breast Cancer Research Group:
Dr. Masakazu Toi

National Cancer Institute of Canada –Cancer Trials Group:
Prof. Tim Whelan

National Cancer Research Institute Breast Cancer Studies Group:
Prof. Alastair Thompson

Swedish Breast Group:
Prof. Per-Olof Malmstrom

Swiss Group for Clinical Cancer Research:
Dr Olivia Pagani

Trans-Tasman Radiation Oncology Group:
Associate Prof. Boon Chua

Appendix XI Compatibility with Other Studies

Given the number of breast cancer trials running in the UK it is important to avoid the problem of “over-burdening” patients with trial choices. The SUPREMO trial should be compatible with most current non-interventional breast cancer studies and will not be applicable to the same patient population as any treatment trials for non-invasive or metastatic disease.

Quality of Life Substudy

However patients entered into the SUPREMO Quality of Life sub-study should not be enrolled into another trial’s QoL sub-study.

Similarly, if they have already been enrolled into an ongoing QoL study of another trial they should not be entered into SUPREMO QoL substudy.

Please refer to the SUPREMO website (www.supremo-trial.com) for a current list of trials that are compatible with SUPREMO.

Appendix XII Abbreviations

AC	Adriamycin and Cyclophosphamide
BNP	B Type Natriuretic Peptide
CAF	Cyclophosphamide, Adriamycin and 5-fluorouracil
CD	Compact Disk
CEF	Cyclophosphamide, Epirubicin and 5-fluorouracil
CI	Confidence Interval
CMF	Cyclophosphamide, Methotrexate and 5-fluorouracil
CT	Computed Tomography
CT-Sim	Computed Tomography- simulator
CTV	Clinical Target Volume
DCIS	Ductal Carcinoma In Situ
DICOM	Digital Imaging and Communications in Medicine
Dmax	Maximum Dose
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EC	Epirubicin and Cyclophosphamide
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EpiCMF	Epirubicin and Cyclophosphamide, Methotrexate and 5-fluorouracil
LCIS	Lobular Carcinoma In Situ
ER	Oestrogen Receptor
FAC	5-fluorouracil, Adriamycin and Cyclophosphamide
FEC	5-fluorouracil, Epirubicin and Cyclophosphamide
GP	General Practitioner
Gy	Gray
H&E	Haematoxylin & Eosin
GCP	Good Clinical Practice
ICRU 50	International Commission on Radiation Units
IGF-1	Insulin-Like Growth factor-1
IMC	Internal Mammary Chain
IPEM	Institute of Physics and Engineering in Medicine
ISD	Information Services Division
LRF	Loco-regional Failure
LRR	Loco-regional Recurrence
LVD	Left Ventricular Dysfunction
MSCF	Medial Supraclavicular Fossa
MV	Mega Voltage
NIH	National Institutes of Health
NSABP	National Surgical Adjuvant Breast and Bowel Project
NHS	National Health Service
PMRT	Postmastectomy Radiotherapy
PTV	Planning Target Volume
QA	Quality Assurance
QC	Quality Control

QALY	Quality-Adjusted Life-Year
QoL	Quality of Life
RR	Relative Risk
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SEER	Surveillance Epidemiology and End Results
SIGN	Scottish Intercollegiate Guidelines Network
START	Standardisation of Breast Radiotherapy Trial
TAD	Target Absorbed Dose
TLD	Thermo Luminescent Dosimetry
TNM	Tumour, Node, Metastasis (Clinical Classification)
UICC	International Union Against Cancer
VEGF	Vascular Endothelial Growth Factor
TRAM	Transverse Rectus Abdominis Muscle
DNA	Deoxyribonucleic Acid
mRNA	Messenger Ribonucleic Acid
RNA	Ribonucleic Acid
MAPK	Mitogen-Activated Protein Kinase
GST	Glutathione S-Transferase
ATM	Ataxia Telangiectasia Mutated
PARP	Poly (ADP-ribose) Polymerase
ADP	Adenosine Diphosphate
TMA	Tissue Microarray
MALDI-TOF	Matrix-assisted Laser Desorption-Ionisation Time Of Flight
MLSO	Medical Laboratory Scientific Officer
IHC	Immunohistochemistry
FISH	Fluorescent <i>In Situ</i> Hybridisation
CART	Classification And Regression Trees
BIS	Body Image Scale
HADS	Hospital Anxiety and Depression Scale
LD flap	Latissimus Dorsi flap
EQ	EuroQol
NTCP	Normal Tissue Compliance Probability
EDTA	Ethylenediamine Tetraacetic
sn	Sentinel node
ITC	Isolated Tumour Cell
HER2	HER2/neu protein
ICH-GCP	International Conference on Harmonisation of Good Clinical Practice

Necessary Additional Data- statistical plan

[Click here to download Necessary Additional Data: QoL Statistical Analysis Plan v2.3 20Jan2017 signed.docx](#)

CONSORT checklist

[Click here to download Necessary Additional Data: Velikova CONSORT 2010 Checklist.doc](#)

List of co-investigators

[Click here to download Necessary Additional Data: UK co-investigators SUPREMO QOL.xlsx](#)